#18

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re:	US Patent No. 5,202,333
Issued:	April 13, 1993
Application No:	07/704,565
Filed:	May 22, 1991
Inventors:	Jacob Berger *et al.*
Assignee:	Roche Palo Alto LLC
For:	Tricyclic 5-HT_3 antagonists

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Application for extension of patent term under 35 USC 156(d)(1)

Roche Palo Alto LLC, a Delaware limited liability company, is the assignee of the entire interest in US Patent No. 5,202,333, issued on April 13, 1993, for Tricyclic 5-HT_3 antagonists, by an assignment from the inventors, Jacob Berger et al., to Syntex (U.S.A.) Inc. recorded on September 13, 1991 at Reel 005829, Frame 0428; the subsequent merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC, recorded on July 9, 2003 at Reel 013782, Frame 0352; and the subsequent change of name of Syntex (U.S.A.) LLC to Roche Palo Alto LLC, recorded on July 10, 2003 at Reel 013782, Frame 0874. An executed power of attorney and statement pursuant to 37 CFR § 3.73, signed by Nancy M. Cohen, Vice President and Secretary, is attached to this application at Attachment A.

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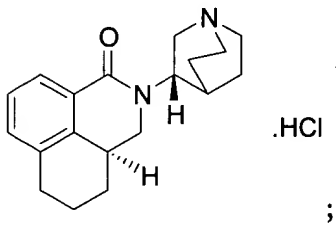
Roche Palo Alto LLC submits this application for extension of the patent term of US Patent No. 5,202,333 by providing the following information, as required by 35 USC 156 and 37 CFR 1.710 *et seq.*

1. Complete identification of product

The approved product is Aloxi™ (palonosetron hydrochloride) injection.

It comprises a compound having:

(a) the structural formula:



;

(b) the molecular formula: $C_{19}H_{24}N_2O.HCl$;

(c) the molecular weight: 332.87;

(d) the chemical names:

(1) (3a*S*)-2,3,3a,4,5,6-hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one monohydrochloride

[from the 2003 *USP Dictionary of USAN and International Drug Names*];

(2) 2-(1-azabicyclo[2.2.2]oct-3*S*-yl)-2,3,3a*S*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one hydrochloride

[from US Patent No. 5,202,333, e.g. at claim 32]; and

(3) (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo [2,2,2] oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride

[from the proposed labeling for Aloxi™, Attachment H];

(e) the generic names:

palonosetron hydrochloride (USAN) and

palonosetron (INN); and

(f) the CAS registry numbers:

135729-62-3 (palonosetron hydrochloride) and

135729-56-5 (palonosetron).

2. Identification of Federal statute/provision of law

Aloxi™ (palonosetron hydrochloride) injection was subject to regulatory review under 21 USC 355(b)(1) [§505(b)(1) of the Federal Food, Drug and Cosmetic Act].

3. Date on which product received permission for commercial marketing or use

Aloxi™ (palonosetron hydrochloride) injection received permission for commercial marketing under 21 USC 355(b)(1) on July 25, 2003.

4. Identification of active ingredient

Aloxi™ (palonosetron hydrochloride) injection contains as its sole active ingredient palonosetron hydrochloride, described above in item 1. To the best of applicant's knowledge, this product has not previously been approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. Time period for submitting application

This application for extension of patent term is being submitted within the period permitted for submission under 35 USC 156(d)(1)(A), i.e. the sixty day period beginning on the date the product received permission for commercial marketing. This period began on July 25, 2003 and ends on September 23, 2003.

6. Identification of patent

The patent for which patent term extension is being sought is US Patent No. 5,202,333, "Tricyclic 5-HT_3 Receptor Antagonists", inventors Jacob Berger , Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, which issued on April 13, 1993. The term of US Patent No. 5,202,333 will expire, unless extended, on April 13, 2010, seventeen years from the date on which the patent was issued.

7. Copy of patent

A complete copy of US Patent No. 5,202,333, including specification and claims, is attached as Attachment B.

8. Other patent documents

The fourth and eighth year maintenance fees have been paid; and copies of the maintenance fee statements (from the Patent & Trademark Office Web site) verifying the payments are attached as Attachment C. The twelfth year maintenance fee may not be paid until April 13, 2004 at the earliest, and may be paid as late as April 13, 2005 with a surcharge.

No disclaimer, Reexamination Certificate, or Certificate of Correction has issued in US Patent No. 5,202,333.

A copy of the Notice of Recordation and assignment from the inventors to Syntex (U.S.A.) Inc. is attached as Attachment D.

A copy of the Notice of Recordation and Certificate of Merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC is attached as Attachment E.

A copy of the Notice of Recordation and Certificate of Amendment changing the name of Syntex (U.S.A.) LLC into Roche Palo Alto LLC is attached as Attachment F.

9. Claims covering the product

US Patent No. 5,202,333 claims Aloxi™ (palonosetron hydrochloride) injection in the following applicable claims:

Claim 1 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of the compound of Formula 1 in which the optional double bond is absent, n is 2, p and q are each 0, and R^3 is a group of formula (b) in which u is 0 and z is 2].

Claim 2 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 1 in which both q and u are 0, and p is 0].

Claim 3 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 2 in which p is 0].

Claim 4 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 3 in which R^3 is 1-azabicyclo[2.2.2]oct-3-yl].

Claim 27 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 4 in which the optional double bond is absent].

Claim 29 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 27 in which n is 2].

Claim 30 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 29 in which R^3 is 1-azabicyclo[2.2.2]oct-3-yl, named as 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one].

Claim 31 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of a compound of claim 30 which is 2-(1-azabicyclo[2.2.2]oct-3*S*-yl)-2,3,3a*S*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one].

Claim 32 covers palonosetron hydrochloride [a compound of claim 31 which is 2-(1-azabicyclo[2.2.2]oct-3*S*-yl)-2,3,3a*S*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one hydrochloride].

Claim 40 covers, *inter alia*, a composition for treating emesis [a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain] comprising a therapeutically effective amount of palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of the compound of claim 1 in which the optional double bond is absent, n is 2, p and q are each 0, and R^3 is a group of formula (b) in which u is 0 and z is 2] in combination with a pharmaceutically acceptable carrier.

Claim 41 covers, *inter alia*, a method for treating emesis [a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain] in an animal in need of such treatment, comprising administering a therapeutically effective amount of palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of the compound of claim 1 in which the optional double bond is absent, n is 2, p and q are each 0, and R^3 is a group of formula (b) in which u is 0 and z is 2] to such animal.

Claim 46 covers, *inter alia*, a method for treating emesis in an animal in need of such treatment, comprising administering a therapeutically effective amount of palonosetron hydrochloride to such animal [a method of claim 41 in which the condition is emesis].

Claim 47 covers, *inter alia*, a method for treating emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, comprising

administering a therapeutically effective amount of palonosetron hydrochloride to such human [a method of claim 46 in which the condition is emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis].

10. Relevant dates and information pursuant to 35 USC 156(g)

The relevant dates and information under 35 USC 156(g) and 37 CFR 1.740(a)(10)(i) are as follows:

(A) December 22, 1992: Effective date of IND 39,797;

(B) September 27, 2002: Submission date of NDA 21-372; and

(C) July 25, 2003: Approval date of NDA 21-372.

11. Brief description of significant activities

A brief description of the significant activities undertaken during the regulatory review period is set forth below in chart form. Please note that IND 39,797 was filed by Syntex (U.S.A.) Inc., the predecessor company to Roche Palo Alto LLC [see the Certificate of Merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC in Attachment E and the Certificate of Amendment changing the name of Syntex (U.S.A.) LLC to Roche Palo Alto LLC in Attachment F]. The IND was transferred by Syntex (U.S.A.) Inc. to Helsinn Healthcare SA on August 3, 1998; and NDA 21-372 was submitted by Helsinn Healthcare SA. An authorization from Helsinn Healthcare SA to Roche Palo Alto LLC to rely upon the activities of Helsinn Healthcare SA before the US Food and Drug Administration during the regulatory review period in making its applications for extension of patent term, and granting the Commissioner of Food and Drugs and the Commissioner for Patents the right to refer to IND 39,797 and NDA 21-372 in determining the eligibility of Roche Palo Alto LLC for such extensions, is attached as Attachment G. Helsinn Healthcare SA is licensed under U.S. Patent No. 5,202,333.

Date		Document	Summary
June 6, 1992	IND 39,797	Submission of FDA 1571 Form	Original submission – notice of claimed investigational exemption for intravenous administration of a novel, selective 5-hydroxytryptamine receptor 3 antagonist. RS 25259.
June 18, 1992	IND 39,797	Letter from FDA	Acknowledgement of receipt of new IND submitted and assigning number
July 7, 1992	IND 39,797	Telephone Call from FDA	Notification of clinical hold for IND 39,797.
July 15, 1992	IND 39,797	Letter from FDA	Statement that the proposed study under this IND may not be initiated because of deficiencies. The information is insufficient.
July 31, 1992	IND 39,797	Letter to FDA (Serial 001)	Partial response to FDA requests for information in the 7/15/92 letter
September 30, 1992	IND 39,797	Letter from FDA	FDA letter from S. Fredd providing list of information needed in order to initiate the clinical study.
October 16, 1992	IND 39,797	Letter from FDA	FDA comments, recommendations and requests re the chemistry portion of the submission.
November 9, 1992	IND 39,797	Letter to FDA (Serial 002)	Complete response to clinical hold issues. Syntex conducted two additional pre-clinical studies to further elucidate the effects of RS 25259-197 on cardiac conduction and on the autonomic nervous system.
December 22, 1992	**IND 39,797**		**Telephone call from FDA confirming clinical hold is lifted. Effective date of IND application.**
January 15, 1993	IND 39,797	Serial 003	Submission of preclinical in vitro study utilizing RS 42358-197 entitled "An In Vitro Assessment of the Cardiotoxic Effects of 5-HT3 Receptor Antagonists". The results of the abstract suggest that RS 42358 is cytotoxic in an in vitro preparation of rat cardiac mycocytes.
January 20, 1993	IND 39,797	Serial 004 (Protocol Amendment)	New Protocol and Investigators for study RGR 2092 entitled "A Single Ascending Dose Safety nd Pharmacokinetics Study of IV RS25259 in Healthy Volunteers".
January 22, 1993		Amendment # 005	Submitting to FDA a report supporting a change

	IND 39,797	(Chemistry/Microbiology)	in the packaging container for RS 25259 IV Solution.
March 15, 1993	IND 39,797	Amendment # 007 (Chemistry/Microbiology)	Information Amendment: Submission of changes to the synthetic scheme
April 28, 1993	IND 39,797	Amendment # 010 (Protocol Amendment)	Change in the Protocol for study RGR 2092
June 1, 1993	IND 39,797	Amendment # 011 (Protocol Amendment)	New Protocol for study RFR 2216 entitled "Plasma, Pharmacokinetics, Metabolism and Excretion IV[14C]197 After Intravenous Injection"
July 21, 1993	IND 39,797	Amendment # 015 (Protocol Amendment)	Change in Protocol for study RGR 2092 .
August 6, 1993	IND 39,797	Amendment # 016	ANNUAL REPORT (June 3, 1992 - March 2, 1993)
October 4, 1993	IND 39,797	Amendment # 018 (Protocol Amendment)	New Protocol and Investigators for study RGR/259s2120/USA entitled: "A Safety, Antiemetic Efficacy and Pharmacokinetic Study of Single dose IV RS25259-197 in Cisplatin-Naïve Cancer Patients Receiving High-Dose Cisplatin Chemotherapy".
November 19, 1993	IND 39,797	Amendment # 020 (Protocol Amendment)	New Clinical Investigator for study RGR/259s2120/USA.
December 23, 1993	IND 39,797	Amendment # 021 (Protocol Amendment)	Change in Protocol: for study 2120. Referencing FDA letter 11/2/93. Response to Division comments.
February 4, 1994	IND 39,797	Amendment # 022 (Pharmacology/Toxicology)	Information Amendment: Report AT 6161.
February 11, 1994	IND 39,797	Amendment # 023 (Chemistry/Microbiology)	Information Amendment: Synthesis route changed .
February 14, 1994	IND 39,797	Amendment # 024 (Protocol Amendment)	New Protocol and Investigators for study 25259s2500 entitled "A Dose Ranging Safety and Efficacy Comparison of Four Dose Levels of Intravenous RS-25259 to Placebo in the Prevention of Postoperative Nausea and Vomiting Following Abdominal and Vaginal Hysterectomy".
March 4, 1994	IND 39,797	Amendment # 025	New Investigator for study 25259s2500
March 24, 1994	IND 39,797	Amendment # 026 (Protocol Amendment)	New Protocol and Investigator for study 25259s2330 entitled "A Dose Ranging Efficacy, Safety and Pharmacokinetic Study of Single Intravenous Doses of RS25259 for Prevention of Nausea and Vomiting in Chemotherapy-Naïve Cancer Patients Receiving Highly Emetogenic Chemotherapy".
April 6, 1994	IND 39,797	Amendment # 027 (Protocol Amendment)	New Investigator for study 25259s2500 New Investigator for study 25259s2330
May 5, 1994	IND 39,797	Amendment # 028 (Protocol Amendment)	New Investigator for study 25259s2500

June 1, 1994	IND 39,797	Amendment # 029 (Protocol Amendment)	New Investigator for study 25259s2330 New Investigator for study 25259s2500 Information Amendment: Pharmacology / Toxicology: Databank Report AT 6664.
June 1, 1994	IND 39,797	Amendment # 030 (Pharmacology/Toxicology)	Information Amendment: final report AT 6655. Other: Draft protocol. Proposed 2 year protocol entitled "Oral Gavage Carcinogenicity Study with RS 25259-197 in Rats".
June 27, 1994	IND 39,797	Amendment # 031 (Protocol Amendment)	Change in Protocol for study 25259s2330
July 5, 1994	IND 39,797	Amendment # 032	Information Amendments Chemistry /Microbiology: Changes to CMC re: batch PA 17555-103 of RS25259-197. Pharmacology /Toxicology: final report filed to this IND and cross referenced to IND 42,886/018 CL 6721. Final report AT 6664 supercedes final report AT 6000. Clinical: additional clinical study site for study 25259s2330. New Investigator for study 25259s2330.
July 22, 1994	IND 39,797	Amendment # 033	ANNUAL REPORT (March 3, 1993 – March 2, 1994)
August 2, 1994	IND 39,797	Amendment # 034 (Chemistry/Microbiology)	Information Amendment: Alternate route synthesis for RS 25259-197, lot PA 17555-103 and lot PA 17555-53.
August 5, 1994	IND 39,797	Amendment # 035	Information Amendment (Clinical): New name of clinical site. New Investigator for study 25259s2330. New Investigator for study 25259s2500 Pharmacology /Toxicology: preclinical report filed to IND 42,886/021 and cross reference to this IND AT 6700.
August 15, 1994	IND 39,797	Amendment # 036 (Protocol Amendment)	Change in Protocol for study 25259s2500 Change in Protocol for study 25259s2330
September 5, 1994	IND 39,797	Amendment # 037	Chemistry /Microbiology: annual stability statement for RS25259-197 IV Solution. Clinical: clinical laboratory update for protocol 25259s2330; New Investigator for study 25259s2330
October 6, 1994	IND 39,797	Amendment # 038	New Investigator for study 25259s2330 Pharmacology /Toxicology: preclinical report filed to this IND. AT 6750 & AT 6751.
October 14, 1994	IND 39,797	Amendment # 039	Proposed carcinogenicity protocol.
November 1, 1994	IND 39,797	Letter from FDA	Letter to M. Reitman from S. Fredd re: comments and recommendations re: 3-months dose ranging study and carcinogenicity study protocol.
November 9, 1994	IND 39,797	Amendment # 040 (Information and Protocol Amendments)	New Investigator for study 25259s2330 Chemistry /Microbiology: letter detailing additional manufacturing site, including analytical

			test results, synthetic description and scheme and stability statement. Pharmacology /Toxicology: preclinical reports AT 6777, AT 6755 & AT 6756.
December 5, 1994	IND 39,797	Amendment # 041 (Protocol Amendment)	New Investigator for study 25259s2330
December 7, 1994	IND 39,797	Amendment # 042	Safety Report Study 25259s2332,
January 6, 1995	IND 39,797	Amendment # 043 (Pharmacology/Toxicology)	Information Amendment: final preclinical report filed to IND 42,886/028 and cross referenced to this IND. AT 6787.
February 6, 1995	IND 39,797	Amendment # 044 (Protocol Amendment)	New Investigator for study 25259s2300
February 23, 1995	IND 39,797	Amendment # 045 (Clinical)	Information Amendment: final clinical report filled to this IND. CL 6951.
March 6, 1995	IND 39,797	Amendment # 046 (Protocol Amendment)	New Investigator for study 25259s2330 Information Amendment (Clinical): addition of clinical lab and/or research facilities.
March 14, 1995	IND 39,797	Letter from FDA	Letter to G. Rouleux from S. Fredd re: mouse carcinogenicity study comments.
April 10, 1995	IND 39,797	Amendment # 047 (Protocol Amendment)	New Investigator for study 25259s2330 Information Amendment (Clinical): Addition of clinical laboratory facility to be used in study 25259s2330.
September 25, 1995	IND 39,797	Amendment # 049 (Chemistry/Microbiology)	Information Amendment re: Stability statement of drug substance stability and analytical method. Other: Notification of new clinical/safety monitor, K. Friday.
May 24, 1996	IND 39,797	Amendment # 050 (Pharmacology/Toxicology)	Information Amendment: Preclinical reports submitted in full to the IND for the first time: AT 6824 AT 6976
August 1, 1996	IND 39,797	Amendment # 051	ANNUAL REPORT (March 3, 1995 through March 2, 1996)
July 31, 1997	IND 39,797	Amendment # 052	ANNUAL REPORT (March 3, 1996 through March 2, 1997)
July 23, 1998	IND 39,797	Amendment # 053	ANNUAL REPORT (March 3, 1997 through March 2, 1998)
July 31, 1998	IND 39,797	Amendment # 054	Transfer of Ownership from Syntex (U.S.A.) Inc. to Helsinn SA.
August 3, 1998	IND 39,797	Amendment # 055	Transfer of Syntex IND 39,797 (RS-25259-197, Palonosetron) to Helsinn Healthcare SA.
September 29, 1998	IND 39,797	Telephone to Kati Johnson	IND 39,797 program input; end of phase 2 meeting information. IND 42,886 program status.
November 12, 1998	IND 39,797	Amendment # 056	Preclinical program background package.
December 23, 1998	IND 39,797	Amendment # 057	Request for End of Phase 2 meeting.
January 19, 1999	IND 39,797	Fax from FDA	EOP2 meeting scheduled for March 15, 1999.
January 27, 1999	IND 39,797	Amendment # 058	Preclinical program background package; information to Amendment # 56.
February 1, 1999	IND 39,797	Letter from FDA	Request for further information to complete change of sponsorship (Serials # 54 and # 55).

February 5, 1999	IND 39,797	Fax from FDA	EOP2 meeting scheduled for March 10.
February 15, 1999	IND 39,797	Amendment # 059	Background Document for March 10, 1999 End of Phase 2 meeting.
March 2, 1999	IND 39,797	Telephone from Ms. McNeil	Studies 2500 and 2502 efficacy results
March 4, 1999	IND 39,797	Fax to FDA	Desk copy of studies 2500 and 2502.
March 8, 1999	IND 39,797	Telephone to Dr. Goldkind	Reviewer comments.
March 19, 1999	IND 39,797	Meeting	End-of-Phase 2 Meeting with FDA.
March 29, 1999	IND 39,797	Amendment # 60	Reply to FDA letter of February 1, 1999 about the change of Sponsorship.
April 29, 1999	IND 39,797	Letter from FDA	FDA comments and recommendations referred to amendments # 56 and # 58 and the EOP2
May 7, 1999	IND 39,797	Amendment # 062	Revised study termination report-Syntex carcinogenicity study in mice; Cross-reference to IND 42,886 Palonosteron Hydrochloride Oral.
May 21, 1999	IND 39,797	Letter from FDA	EOP2 biopharmaceutics conference call meeting minutes.
August 19, 1999	IND 39,797	Amendment # 064	Phase 3 and Commercial Formulation.
September 24, 1999	IND 39,797	Amendment # 065	Annual Report.
October 15, 1999	IND 39,797	Amendment # 066	PALO 99-08, CLE 1063/1 "Palonosteron Hydrochloride: 26 Week Intravenous Administration Toxicity Study in the Rat with a 4 Week intravenous-free Period". IND Safety Report: Initial Written report.
November 24, 1999	IND 39,797	Amendment # 068	Phase 3 efficacy protocol PALO 99-03. Request for Special Protocol Assessment and Agreement.
November 24, 1999	IND 39,797	Amendment # 069	Phase 3 efficacy protocol PALO 99-04. Request for Special Protocol Assessment and Agreement.
November 30, 1999	IND 39,797	Amendment # 070	Toxicology study PALO-99-08; CLE-1063/1 Information Amendment: Follow-up and Additional Information to IND Safety Report, IND Amendment # 66.
December 10, 1999	IND 39,797	Amendment # 071	Phase 3 efficacy protocol PALO 99-05. Request for Special Protocol Assessment and Agreement.
December 22, 1999	IND 39,797	Amendment # 072 (Protocol Amendment)	New protocol, PALO 99-39 Phase 1 ADME study.
April 7, 2000	IND 39,797	Amendment # 074 (Protocol Amendment)	New Protocols, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05.
April 24, 2000	IND 39,797	Amendment # 075	Proposed Pediatric Study Request (PPSR).
April 26, 2000	IND 39,797	Amendment # 076	Phase 3 efficacy protocol PALO 00-01. Request for Special Protocol Assessment and Agreement.
May 22, 2000	IND 39,797	Amendment # 077 (Protocol Amendment)	New protocol, Phase 3 Protocol PALO-99-06.
June 5, 2000	IND 39,797	Amendment # 078	Request for teleconference with Pharm/Tox Reviewer to Discuss Segment 3 Reprotox Study.
June 9, 2000	IND 39,797	Letter from FDA	FDA response to the PALO-00-01 FDAMA special protocol review request.

June 14, 2000	IND 39,797	Letter from FDA	Reply to June 5 and 6, 2000 correspondence requesting a meeting to discuss the acceptability of a completed Segment 3 pre- and post-natal study of palonosetron in rats.
June 19, 2000	IND 39,797	Amendment # 079 (Protocol Amendment)	New Investigators, Phase 3 protocols PALO-99-03, PALO-99-04, PALO-99-05, PALO-99-06.
June 30, 2000	IND 39,797	Amendment # 080	IND Safety Report-In-Vitro Purkinje Fiber Dog Data.
July 19, 2000	IND 39,797	Amendment # 081 (Protocol Amendment)	New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, PALO-99-06.
August 4, 2000	IND 39,797	Amendment # 082	Follow up to IND Safety Report – In Vitro Purkinje Fiber Dog Data (IND Amendment # 80, submitted June 30, 2000).
August 9, 2000	IND 39,797	Letter from FDA	FDA reply to amendment dated June 30, 2000 (serial # 80).
August 14, 2000	IND 39,797	Amendment # 083 (Protocol Amendment)	New protocol, Pediatric Protocol PALO-99-07.
August 17, 2000	IND 39,797	Telephone to Melodi McNeil	Dr. Talarico's letter (received today) dated August 9, 2000, regarding our original plans to exclude patients from phase 3 trials who are taking comeds which prolong QTc.
August 18, 2000	IND 39,797	Amendment # 084 (Protocol Amendment)	New investigators, Phase 3 Protocols PALO-99-04, PALO-99-05, PALO-99-06.
August 24, 2000	IND 39,797	Amendment # 085 (information Amendment)	Chronic Toxicology Draft Reports for Palonosetron, 9-month in Dog, 26-week in Rat.
August 24, 2000	IND 39,797	Amendment # 086	New Protocols, Phase 1 protocols PALO-99-35 and PALO-99-51.
August 24, 2000	IND 39,797	Telephone to Melodi McNeil	Serial # 82 Follow-up to Safety Report (Serial # 80), plan to allow comeds which prolong QTc in Phase 3 Trials.
August 29, 2000	IND 39,797	Amendment # 087	Phase 1 protocols PALO-99-35 and PALO-99-51.
September 8, 2000	IND 39,797	Amendment # 088 (Information Amendment)	ReproTox Final Reports for Palonosetron.
September 20, 2000	IND 39,797	Amendment # 090	New Investigators PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.Change in Protocols, Protocol Amendment No. 2 for PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
September 26, 2000	IND 39,797	Amendment # 091 (Protocol Amendment)	New Investigators PALO-99-03, PALO-99-05, PALO-99-06, and PALO-99-07.
September 26, 2000	IND 39,797	Letter from FDA	FDA reply to Pediatric Study Request PALO-99-07.
September 28, 2000	IND 39,797	Amendment # 092	IND Annual Report.
October 16, 2000	IND 39,797	Amendment # 093 (Information Amendment)	Rat Carcinogenicity Study PALO-98-03, Decreasing Number of Survivors in High Dose Female Group – Request for Guidance. Gross-

			reference to IND 42,886, Palonosetron Hydrochloride Oral.
November 6, 2000	IND 39,797	Fax to Melodi McNeil (2)	Serial # 93, October 16, 2000 – Request for confirmation of Dr. Choudary's feedback of October 17, 2000 regarding the loss rate in the high dose female group in the Palonosetron Rat Carcinogenicity Study.
November 14, 2000	IND 39,797	Letter from Dr. Talarico	FDA letter from Dr. Talarico (undated and unsigned) postmarked 9 Nov 2000 – FDA evaluation of juvenile rat and dog tox studies, follow-up FDA requests, and FDA request for full reports and data for dog in-vitro and in-vivo CVS studies.
November 17, 2000	IND 39,797	Amendment # 094 (Protocol Amendment)	New Investigators, PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
November 22, 2000	IND 39,797	Amendment # 095 (Request for teleconference)	Request for teleconference to discuss the proposed NDA CMC strategy.
November 30, 2000	IND 39,797	Amendment # 096 (Request for teleconference)	Request for Teleconference to Discuss the Proposed Pediatric Protocol PALO-99-07.
December 12, 2000	IND 39,797	Amendment # 097 (Response to FDA request for information)	Reply to FDA Letter Postmarked November 9, 2000, Regarding the 28-Day Juvenile Rat and Dog Studies and the *in vivo* Dog Cardiovascular Safety Study.
December 15,2000	IND 39,797	Fax from FDA	FDA fax confirmation of CMC Strategy teleconference of Jan 30, 2001
December 18, 2000	IND 39,797	Amendment # 098 (Protocol Amendment)	New Protocol, Phase 1 Protocol PALO-99-34.
December 20, 2000	IND 39,797	Amendment # 099 (Protocol Amendment)	New Investigators, PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
December 26, 2000	IND 39,797	Fax from FDA	FDA fax confirming (1) Pediatric protocol teleconference February 8, 2001, and (2) CMC Strategy meeting January 30th instead of a teleconference.
January 2, 2001	IND 39,797	Amendment # 100	Protocol Amendment, Change in Protocols, Protocol Amendment No. 3 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
January 25, 2001	IND 39,797	Amendment # 103 (New Investigators)	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05 and PALO-99-06.
January 30, 2001	IND 39,797	Meeting	CMC strategy meeting with FDA.
January 31, 2001	IND 39,797	Letter from Dr. Talarico	FDA letter from Dr. Talarico dated 31 Jan 2001 (in electronic signature page) regarding juvenile rat tox data – FDA recommendation that ~07 patients be evaluated for ophthalmic function.

February 8, 2001	IND 39,797	Telephone to Melodi McNeil	FDA agreement with Helsinn's replies (submitted in IND Serial # 96) to FDA's comments and request (FDA letter, 26 Sept 2000) regarding the PALO-99-07 pediatric protocol, and agreement to cancel the FDA/Helsinn Pediatric Protocol teleconference scheduled for 8 Feb 2001.
February 22, 2001	IND 39,797	Telephone to Melodi McNeil	Resuming treatment in the high dose female group, in the Palonosetron rat carcinogenicity study until 20% of the group (n=13) remains as survivors, then discontinue treatment, do not kill the animals, and allow the group to proceed to the end of the 104 week study.
February 23, 2001	IND 39,797	Telephone to Melodi McNeil	Resumption of treatment administration to high dose female rats in the PALO-98-03 rat carcinogenicity study.
February 27, 2001	IND 39,797	Letter from FDA	FDA minutes of Palonosetron NDA CMC strategy meeting held January 30, 2001.
March 8, 2001	IND 39,797	Letter from FDA	FDA letter electronically dated 8 March, 2001 re: FDA's response to our replies of 30 November 2000 (Serial # 96) regarding the pediatric PALO-99-07 protocol.
April 9, 2001	IND 39,797	Telephone to Peggy Hair	Issuance of Palonosetron NDA Number – NDA 21-372.
April 10, 2001	IND 39,797	Amendment # 106 (Pharmacology / Toxicology)	Mouse Carcinogenicity Study PALO-99-18, Decreasing Number of Survivors in Intermediate Dose Female Group – Request for Guidance.
April 10, 2001	IND 39,797	Amendment # 107 (Change in protocol)	Protocol Amendment, Change in protocols, protocol Amendment No. 4 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
April 13, 2001	IND 39,797	Telephone from Melodi McNeil	IND Serial # 106, 10 april 2001, 20 survivors in intermediate female dose group, mouse carcinogenicity study.
April 17, 2001	IND 39,797	Amendment # 108 (Pharmacology / Toxicology)	Information Amendment: Rat carcinogenicity study PALO-98-03, notification of N=13 survivors in high dose female group, request for confirmation to discontinue treatment of this group only.
April 19, 2001	IND 39,797	Amendment # 109 (Clinical)	Information Amendment: IV Dexamethasone Shortage in the US-Request for preliminary FDA Feedback regarding the acceptability using alternative corticosteroid comeds in Phase 3 efficacy Protocol PALO-99-05.
May 30, 2001	IND 39,797	Amendment # 112 (Pharmacology / Toxicology) (Clinical)	Reply to FDA Letter electronically dated 31 January 2001, Regarding the 28-Day Juvenile Rat Study PALO-99-12 and Pediatric Clinical Trial PALO-99-07.
June 19, 2001		Telephone to/from Melodi McNeil	1) Status of FDA feedback re IND Serial # 107 (Protocol Amendment # 4 to PALO-99-03,

	IND 39,797		PALO-99-04, PALO-99-05, and PALO-99-06), 2) Status of FDA feedback re IND Serial # 109 (IV Dexamethasone shortage in the US-alternatives for use in PALO-99-05).
June 25, 2001	IND 39,797	Letter from Dr. L. Talarico	FDA formal acceptance of dex alternative for PALO-99-05.
July 23, 2001	IND 39,797	Amendment # 114 Chemistry, Manufacturing and Controls	New Site (Helsinn Advanced Synthesis) for Drug Substance Manufacture. New Site (SP Pharmaceuticals) for Manufacture of Phase 3 Clinical Supplies. 18-Month Stability for Phase 3 Clinical Supplies manufactured by Oread.
July 30, 2001	IND 39,797	Amendment # 115	Protocol Amendment, Change in Protocols, Protocol Amendment No.5 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06. Request for Change in Documented Special Protocol Assessments.
August 1, 2001	IND 39,797	Amendment # 116	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
August 2, 2001	IND 39,797	Telephone to/from Mr. Brian Strongin	(1) Mr. Brian Strongin, newly appointed FDA Project Manager for the Palonosetron INDs (2) 45-day clock for Special Protocol Review of Serial # 115, Protocol Amendment # 5 to PALO-99-03, PALO-99-04, and PALO-99-05.
August 2, 2001	IND 39,797	Amendment # 117	Telephone (faxed) Safety Report – Anaphylactic Reaction, Patient # 1211 in phase 3 trial PALO-99-06 (open label safety study).
August 3, 2001	IND 39,797	Letter from Dr. L. Talarico	FDA letters received re: Serial # 107 (Protocol Amendment # 4).
August 3, 2001	IND 39,797	Letter from Mr. Brian Strongin	Acknowledgement of receipt of Amendment Serial # 115 (Protocol Amendment # 5) to PALO-99-03, PALO-99-04 and PALO-99-05.
August 14, 2001	IND 39,797	Telephone to Mr. Brian Strongin	Notification of pending correction to protocol amendment # 5 to PALO-99-03, PALO-99-04, PALO-99-05 and PALO-99-06.
August 23, 2001	IND 39,797	Amendment # 118	Protocol Amendment, Change in Protocols, Correction to Protocol Amendments No. 5 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06. Request for Change in Documented Special Protocol Assessment.
August 23, 2001	IND 39,797	Amendment # 119	IND Safety Report – Acute Psychosis, Patient # 3454 in Phase 3 trial PALO-99-03.
August 24, 2001	IND 39,797	Amendment # 120	Information Amendment – Pharmacology: Summary Review and Reports of Palonosetron Pre-clinical Cardiovascular Safety (CVS) Studies.
August 27, 2001	IND 39,797	Amendment # 121	Request for Meeting to Review and Discuss the Palonosetron Pre-clinical Cardiovascular Safety (CVS) Program.
August 28, 2001	IND 39,797	Letter from Mr. Brian Strongin	FDA letter re receipt of Serial # 118, Protocol Amendment # 5 resubmission for Protocols

			PALO-99-03, PALO-99-04, and PALO-99-05.
September 6, 2001	IND 39,797	Amendment # 122	Request for teleconference to clarify FDA statistical feedback in FDA Special Protocol Assessment reply letters dated January 10, 2000, January 10, 2000, and January 27, 2000, respectively, regarding phase 3 efficacy protocols PALO-99-03, PALO-99-04, and PALO-99-05.
September 19, 2001	IND 39,797	Amendment # 123	Information Amendment: Pharmacology-Toxicology, Final Report PALO-00-19, Entitled, "Palonosetron Hydrchloride: ECG measurements from 28 Day Intravenous Administration Toxicity Study (PALO-99-22; Covance Study Number 1063/17) in the Juvenile Dog".
September 20, 2001	IND 39,797	Amendment # 124	Follow-up to IND Safety Report, Serial # 80, June 30, 2000. Retrospective Evaluation of ECG Tracing Collected During the Phase I and II Development of Palonosetron: Cardiovascular Safety Profile.
September 28, 2001	IND 39,797	Amendment # 125	Request for Pre-NDA Meeting.
October 3, 2001	IND 39,797	Amendment # 126	2001 IND Annual Report.
October 5, 2001	IND 39,797	Letter to Mr. Brian Strongin	Additional desk copies of Serial # 121 for FDA CVS teleconference on November 8, 2001, 1:00 – 2:30 PM.
October 5, 2001	IND 39,797	Letter from Mr. Victor Raczkowski	FDA letter, dated 5 October 2001, re review of submission # 118 (Phase 3 Protocol Amendment # 5).
October 10, 2001	IND 39,797	Amendment # 128	Request for Clinical Pharmacology and Biopharmaceutics Teleconference to Discuss Phase 3 Palonosetron Population PK/PD Protocol PALO-99-33.
October 10, 2001	IND 39,797	Letter from Mr. Victor Raczkowski	Letter from FDA re Request for pre-NDA meeting.
October 15, 2001	IND 39,797	Amendment # 129	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
October 18, 2001	IND 39,797	Fax from FDA / Mr. Brian Strongin	Fax from FDA re statistical teleconference.
October 29, 2001	IND 39,797	Fax from Ms. Helen Wilson	Fax from FDA re Nov. 30, 2001 10-11 AM EST Pop PK/PD teleconference.
November 2, 2001	IND 39,797	Letter from Mr. Brian Strongin	Minutes from the October 18th teleconference.
November 6, 2001	IND 39,797	Telephone to Mr. Brian Strongin	Status of Dr. Choudary's replies to our questions submitted in Serial # 122 (30 May 2001) regarding the juvenile rat tox report.
November 6, 2001	IND 39,797	Telephone to Mr. Hugo Gallo-Torres	Re: Communication Record re Serial # 124, Assessment of Phase 1 and 2 ECGs.
November 21, 2001	IND 39,797	Amendment # 130	IND Safety Report – Rat Carcinogenicity Data.

November 21, 2001	IND 39,797	Fax to Mr. Brian Strongin	Re: Status of Palonosetron Biopharmaceutics Program as requested by FDA in preparetion for the upcoming population PK/PD teleconference scheduled for November 30, 2001.
November 27, 2001	IND 39,797	Fax from Mr. Brian Strongin	Teleconference regarding Palo-99-33 Protocol. Responses to HHC's questions.
December 4, 2001	IND 39,797	Fax from Mr. Brian Strongin	Response to Questions Regarding the Interconversion Study.
December 10, 2001	IND 39,797	Amendment # 131	Reply to FDA Minutes, and Sponsor's Minutes, FDA Statistical Teleconference held October 18, 2001 in follow-up to the Special Protocol Assessments.
December 11, 2001	IND 39,797	Amendment # 132	Protocol Amendment, Change in Protocols, Protocol Amendment # 6 to Phase 3 Clinical Protocols PALO-99-04 and PALO-99-05. Request for Change in Documented Special Protocol Assessments.
December 17, 2001	IND 39,797	Fax from Mr. Brian Strongin	FDA Minutes, preclinical CVS meeting held on 8 November 2001.
December 17, 2001	IND 39,797	Amendment # 133	Notification to FDA of discontinuation of an investigator from IND clinical trials.
December 26, 2001	IND 39,797	Letter from FDA	Officials minutes, meeting held on November 30, 2001.
January 8, 2002	IND 39,797	Amendment # 134	Sponsor's Minutes, FDA Pop PK/PD Teleconference held November 30, 2001.
January 8, 2002	IND 39,797	Amendment # 135	Sponsor's Minutes, Preclinical Cardiovascular Safety Teleconference held November 8, 2001.
January 8, 2002	IND 39,797	Amendment # 136	Information Amendment – Reply to FDA Letter Dated August 3, 2001.
January 11, 2002	IND 39,797	Amendment # 137	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-04, PALO-99-05, and PALO-99-06.
January 16, 2002	IND 39,797	Amendment # 138	Reply to FDA's phoned questions of January 14, 2002, regarding Protocol Amendment # 6 to PALO-99-04 and PALO-99-05 (Serial # 132 dated December 11, 2001).
January 17, 2002	IND 39,797	Telephone to Mr. Kairy Malek	FDA request for Palonosetron protocols and all protocol amendments, plus monitoring reports for all Palonosetron studies performed at Dr. Kovacs site.
January 24, 2002	IND 39,797	Letter from FDA	FDA letter dated 24th January 2002 re: FDA minutes, Palonosetron Stats teleconference held with FDA 18th October, 2001.
January 24, 2002	IND 39,797	Letter from FDA	FDA Special Protocol Assessment letter concerning Protocol Amendment # 6 for PALO-99-04 and PALO-99-05.
January 24, 2002	IND 39,797	Letter from FDA	FDA minutes of stats teleconference held 18th October, 2001.
January 28, 2002	IND 39,797	Letter from FDA	FDA letter dated 28th January, Re: Juvenile rat toxicology study-FDA feedback.

January 29, 2002	IND 39,797	Amendment # 139	Information Amendment – Plans to Perform Additional Pre-Clinical Cardiovascular Safety (CVS) Studies.
February 7, 2002	IND 39,797	Amendment # 140	Request for Pre-NDA Meeting.
February 12, 2002	IND 39,797	Amendment # 141	Protocol, protocol amendments and monitoring-related documents associated with Dr. Kovacs'site.
February 21, 2002	IND 39,797	Amendment # 142	Reply and request, Dr. Raczowski's letter dated 28 January, 2002 regarding 28-day juvenile rat tox study, and ophthalmic function tests in pediatric protocol PALO-99-07.
February 22, 2002	IND 39,797	Fax from Ms. Helen Wilson/FDA	Fax from Ms. Helen Wilson/FDA confirming 10 April 2002 Meeting.
February 28, 2002	IND 39,797	Telephone from Mr. Brian Strongin	FDA feedback regarding timing of ophthalmic exams in PALO-99-07 as requested in Serial # 142.
March 13, 2002	IND 39,797	Amendment # 143	Pre-NDA Meeting Background Package.
March 19, 2002	IND 39,797	Amendment # 144	Labeling information as supplement to IND Serial # 114, SP Pharmaceuticals providing clinical supplies for the phase 3 studies.
March 28, 2002	IND 39,797	Amendment # 145	Protocol Amendment; PALO-99-35 and PALO-99-51
April 1, 2002	IND 39,797	Amendment # 146	Phase 3 Clinical Protocol Amendments: Amendment # 6 to PALO-99-03 and Amendment # 7 to PALO-99-04 and PALO-99-05.
April 2, 2002	IND 39,797	Amendment # 147	Information Amendment: Mouse Carcinogenicity Study PALO-99-18 Final Report.
April 3, 2002	IND 39,797	Amendment # 148	Preliminary Efficacy Data for Pivotal Efficacy Study PALO-99-05 involving highly emetogenic CINV.
April 5, 2002	IND 39,797	Amendment # 149	Request for FDA Review of Proposed Proprietary Names for Palonosetron HCl Intravenous Injection.
April 5, 2002	IND 39,797	Amendment # 150	Follow – up, IND Safety Report Serial # 130 – Final Report, Rat Carcinogenicity Study PALO-98-03. Information Amendment: Submission of (1) PALO-99-38 Final Report, Palonosetron: Unscheduled NDA Synthesis in Rat liver Cells *In Vivo*, (2) PALO-01-16, Summary Results of Chromosomal Aberration Study.
April 8, 2002	IND 39,797	Fax from Mr. Brian Strongin	Responses to questions for the preNDA

			meeting.
April 8, 2002	IND 39,797	Letter from Mr. Victor Raczkowski	Letter from Mr. Victor Raczkowski recommending submission of full reports of PALO-98-03/HS001 and PALO-98-03/HSH002.
April 10, 2002	IND 39,797	Meeting	Pre-NDA Meeting with FDA.
April 22, 2002	IND 39,797	Fax from Mr. Brian Strongin	Request Regarding the Mouse and Rat Carcinogenicity Study Reports Submitted April 2 and April 5, 2002.
April 30, 2002	IND 39,797	Fax to Mr. Brian Strongin	Reply to FDA Request Regarding Mouse and Rat Carcinogenicity Study Reports Submitted April 2 and April 5, 2002 – Identification and Abbreviations in the Reports.
April 30, 2002	IND 39,797	FDA Minutes	FDA Minutes, pre NDA meeting held April 10, 2002.
May 3, 2002	IND 39,797	Amendment # 153	Request for FDA feedback regarding use of the D15 color test in pediatric study PALO-99-07.
May 9, 2002	IND 39,797	Fax to Mr. Brian Strongin	Request for clarification of FM-28 and FM-40 color tests recommended by FDA on 6 May 2002 for use in the PALO-99-07 pediatric trial.
May 20, 2002	IND 39,797	Amendment # 154	Reply to FDA Minutes, Pre-NDA Meeting held April 10, 2002.
May 23, 2002	IND 39,797	Amendment # 155	Sponsor's Minutes, PreNDA Meeting held April 10, 2002.
June 7, 2002	IND 39,797	Fax to Mr. Brian Strongin	Re.: Proposal to submit electronic case report tabulation (CRTs) on CD in the planned Palonosetron NDA.
July 3, 2002	IND 39,797	Fax from Ms. Tawni Schwemer	FDA User's Fees in fiscal year (FY) 2003 (i.e., effective Oct. 1, 2002).
July 24, 2002	IND 39,797	Amendment # 156	Protocol Amendment, New Protocol and Protocol Amendment # 1, Pediatric Protocol PALO-99-07.
September 10, 2002	NDA 21-372	E-mail to Jones / FDA	Helsinn Healthcare SA / User Fee Identification Number: 4391; NDA number 21-732.
September 20, 2002	IND 39,797	Letter from FDA	Status of DMETS review of proposed proprietary name, ALOXI, CINVEX, and

			ONICIT.
September 27, 2002	IND 39,797	Telephone to Mr. Brian Strongin	IND Annual Report, 2002.
September 27, 2002	**NDA 21-372**	**Fax from Chris Celeste**	**Submission of NDA 21-372 acknowledged by FDA.**
October 11, 2002	NDA 21-372	Amendment # 001	Palonosetron Hydrochloride Intravenous Injection, 0.25 mg Amendment # 001.
October 15, 2002	NDA 21-372	Fax to Mr. Brian Strongin	Confirmation of NDA Amendment Submission Addresses Palonosetron NDA 21-372.
October 18, 2002	IND 39,797	Fax from Mr. Brian Strongin	DMETS reviews of the three proposed tradenames for Palonosetron.
November 5, 2002	IND 39,797	Amendment # 157 2002 IND Annual Report	2002 IND Annual Report.
November 7, 2002	NDA 21-372	Letter from Mr. Brian Strongin	FDA letter acknowledging FDA receipt of NDA 21-372.
November 18/19, 2002	NDA 21-372	Telephone from Ele Ibarra-Pratt	Palonosetron clinical study site inspections. information and documentation requested by FDA in preparation for site visits at sites 044 (Ger.), 221 (Russ.) and 212 (Russ.).
November 21, 2002	NDA 21-372	Amendment # 002	Chemistry, Manufacturing and Controls: Letter of Clarification for Helsinn Birex Pharmaceuticals Ltd. To Release Final Product to Commercial Market.
November 26, 2002	NDA 21-372	Telephone from Mr. Brian Strongin	FDA confirmation that Palo NDA has been filed.
November 26, 2002	NDA 21-372	Amendment # 003	Statistical Reviewer Copies of Palonosetron Original NDA Volumes Regarding Rat and Mouse Carcinogenicity Studies.
November 27, 2002	NDA 21-372	Telephone to Ms.Ibarra-Pratt	Site documentation requested by FDA Site # 044 in Germany.
December 2, 2002	NDA 21-372	Fax to Ms.Ibarra-Pratt	Examples of information requested for Palo FDA clinical site inspections in Russia and Germany.
December 9, 2002	NDA 21-372	Telephone to/from Ms.Ibarra-Pratt	FDA request for sponsor representative contact information (not site personnel) near sites # 044, # 212, and # 221 in Germany and Russia for FDA inspectors to contact during inspection of these sites.

December 10, 2002	NDA 21-372	Telephone from Ms.Ibarra-Pratt	Request for site information, US site # 501, Dr. Julio Hajdenberg, New Ritchie, Florida, PALO-99-04 and PALO-99-05 information requested in preparation for FDA site inspection.
December 19, 2002	IND 39,797	Amendment # 158	Pediatric Protocol Amendment: New Investigators for PALO-99-07.
January 14, 2003	NDA 21-372	Fax to Mr. Brian Strongin	Planned four-month safety update for Palonosetron NDA 21-372.
January 20, 2003	IND 39,797	Amendment # 160	Protocol amendment # 2, pediatric protocol PALO-99-07 Information amendment: toxicology, final reports for juvenile rat toxicology study PALO-02-05 and juvenile/neonatal dog toxicology study PALO-99-22.
January 24, 2003	NDA 21-372	Amendment # 004	Four-Month Safety Update.
January 27, 2003	NDA 21-372	Telephone to Ms. Irizarry	Labeling required by FDA for import of DS from HAS (Switzerland) to SP Pharmaceuticals (Albuquerque) for purposes of manufacturing DP validation batches during FDA review (before FDA approval of Palo NDA 21-372.
January 31, 2003	IND 39,797	Telephone from Mr. Brian Strongin	Status of FDA review/reply to sponsor's request for FDA feedback regarding the acceptability of deleting ocular tests from protocol PALO-99-07 as submitted in Serial # 160.
January 31, 2003	IND 39,797	Telephone to Mr. Brian Strongin	Status of requested regarding acceptability of pediatric study PALO-99-07 protocol amendment # 2 (Serial # 160) to remove ocular function tests based on results of juvenile rat and dog tox reports also in Serial # 160.
February 4, 2003	IND 39,797	Amendment # 161	Appeal for reconsideration of proposed tradename ONICIT™.
February 27, 2003	IND 39,797	Amendment # 162	Request for feedback regarding proposed transfer of sponsor's IND obligations involving Helsinn (IND sponsor), MGI (clinical trial manager), and a CRO to conduct a clinical trial.
February 27, 2003	IND 39,797	Amendment # 163	Pediatric protocol amendment: new investigators for PALO-99-07.
March 12, 2003	IND 39,797	Telephone to/from Mr. Brian Strongin	DMETS request for identification of proposed market dose for IV Palo regarding CINVEX proprietary name review. Status of requested FDA review of PALO-99-07 protocol amendment # 2 (IND serial # 160, 20 Jan 03). Status of requested FDA feedback regarding transfer of sponsor's IND obligations, Helsinn-

			MGI-CRO (IND serial # 162, 27 Feb 03).
March 24, 2003	IND 39,797	Amendment # 164	Protocol amendment, new protocol, phase 1 protocol PALO-02-12.
March 27, 2003	IND 39,797	Fax from Dr. Justice	Letter from FDA re: Status Dr. Justice's decision regarding proposed proprietary name CINVEX™; Use of the proposed tradename, ALOXI™; Revision of strength on the immediate container and carton labeling.
April 1, 2003	IND 39,797	Fax from Mr. Brian Strongin	CINVEX™ and ALOXI™ FDA DMETS Reviews.
April 7, 2003	NDA 21-372	Fax to Mr. Strongin	Reply to FDA's fax of April 1, 2003, regarding location of efficacy data for study PALO-00-01 (Study 2330) in Palonosetron NDA 21-372.
April 8, 2003	IND 39,797	Amendment # 165	Pediatric Protocol Amendment: New Investigators for PALO-99-07.
April 8, 2003	NDA 21-372	Fax to Mr. Strongin	Reply to FDA's faxed requests of March 28, 2003 for rat and mouse carcinogenicity studies historical control data and (2) March 28, 2003, a separate fax, requesting clarification of the term "language on diary card" for Study PALO-99-03.
April 9, 2003	NDA 21-372	Amendment # 005	Chemistry, Manufacturing and Controls Contract Analytical Laboratory Change; Drug Product Site of Manufacture Name Change; Stability Update and Request for Extension of Expiration Date: request to extend the expiration date from 24 months to 36 months.
April 11, 2003	NDA 21-372	Telephone to/from Mr. Brian Strongin	FDA DMF deficiency letter faxed to Mr. Franco De Vecchi, US Agent for the DMF.
April 16, 2003	NDA 21-372	Fax to Mr. Strongin	Reply to FDA's faxed statistical requests of March 28, 2003, question # 1, (2) April 1, 2003, question # 2, (3) April 1, 2003, question # 3, and (4) April 7, 2003.
April 17, 2003	IND 39,797	Fax to Mr. Brian Strongin	New information regarding the proposed tradename, ALOXI.
April 21, 2003	NDA 21-372	Fax from Irma Rivera / FDA	Announce an inspection of Helsinn Advanced Synthesis in Biasca by an inspector of the US Food and Drug Administration.
April 24, 2003	NDA 21-372	Amendment # 006	Clinical, Statistical and Pharm/Tox: Replies to FDA faxed questions of March 28, April 1, and April 7, 2003.
April 30, 2003	IND 39,797	Amendment # 166	Chemistry, Manufacturing, and Controls.
May 1, 2003	NDA 21-372	Fax from Mr. Strongin	Statistical information request
May 9, 2003	IND 39,797	Amendment # 167	Pediatric Protocol Amendment: New Subinvestigators for PALO-99-07.

			Subinvestigators for PALO-99-07.
May 22, 2003	NDA 21-372	Teleconference	Statistical teleconference
May 30, 2003	NDA 21-372	Telephone from Mr. Strongin	Acceptability to FDA actions regarding treatment allocation data and proposed permutation testing for PALO-99-03, PALO-99-04, and PALO-99-05, as discussed during the FDA Statistical teleconference held 22 May 03.
June 3, 2003	NDA 21-372	Telephone to Mr. Strongin	Notification to FDA that Helsinn has acquired the name ALOXI and will proceed with the tradename ALOXI. PALO-99-07, Protocol Amendment # 2. Status of phase 3 efficacy treatment allocation information requested by FDA statistical reviewers during FDA statistical teleconference May 22, 2003.
June 4, 2003	IND 39,797	Amendment # 168	Protocol Amendment # 2. Pediatric Protocol PALO-99-07.
June 4, 2003	NDA 21-372	Letter to Mr. Justice	Helsinn acquisition of the tradename Aloxi™.
June 4, 2003	NDA 21-372	Fax from Mr. Strongin	CMC Information Request
June 5, 2003	IND 39,797	Amendment # 169	Investigator's Brochure.
June 6, 2003	NDA 21-372	Letter to Mr. Justice	Sponsor's reply to FDA Reviewing Chemist Dr. Kowblansky's CMC requests of June 5, 2003.
June 9, 2003	NDA 21-372	Amendment # 007	Statistical Information Requested by FDA during the teleconference held May 22, 2003.
June 10, 2003	IND 39,797	Amendment # 170	Protocol Amendment, New Protocol, Phase 1 Protocol PALO-03-05.
June 13, 2003	NDA 21-372	Fax to Mr. Strongin	Sponsor's replies to FDA's pharmacology questions of June 11, 2003.
June 13, 2003	NDA 21-372	Amendment # 008	Chemistry, Manufacturing and Controls (CMC); sponsor's response to CMC questions in FDA's fax dated June 4, 2003.
June 16, 2003	NDA 21-372	Amendment # 009	Statistical information requested by FDA during the teleconference held May 22, 2003; results of permutation tests for PALO-99-03, PALO-99-04 and palo-99-05.
June 17/18, 2003	NDA 21-372	Telephone from Mr. Strongin	FDA request for a CMC teleconference on Thursday, June 19, 2003, 9:00 AM EDT to discuss the Sponsor's reply to FDA's CMC questions of June 4, 2003 (Sponsor's reply in NDA Amendment # 9).
June 18, 2003	NDA 21-372	Amendment # 010	Sponsor's reply to FDA's pharmacology questions of June 11, 2003.
June 20, 2003	NDA 21-372	Amendment # 011	Sponsor's reply to CMC requests in FDA teleconference held June 19, 2003.
June 25, 2003	NDA 21-372	Amendment # 012	Chemistry, Manufacturing and controls: Proposed revisions to immediate container (vial), carton and shipper labels.
June 26, 2003	IND 39,797	Amendment # 171	Proposed pediatric study request.

June 27, 2003	NDA 21-372	Fax to Mr. Strongin	Information request regarding vial label
June 30, 2003	IND 39,797	Amendment # 172	Pediatric Study PALO-99-07; Change in Safety Officer to Sean X. Wang, MD.
June 30, 2003	NDA 21-372	Telephone to/from Mr. Strongin	FDA urgent request for additional of storage conditions to the vials label. Revisions of vial labels. Revisions to vial labels – teleconference with Dr. Kowblansky, FDA Chemistry Reviewer.
July 1, 2003	NDA 21-372	Amendment # 013	Chemistry, Manufacturing and controls: Proposed additional revisions to immediate container (vial) label.
July 3, 2003	NDA 21-372	Fax from Mr. Strongin	Information request regarding QTc Prolongation in Pediatric Patients in PALO-99-07.
July 7, 2003	NDA 21-372	Letter from FDA	FDA minutes of teleconference held June 11, 2003, between representatives of Helsinn Healthcare SA and FDA to obtain clarifications regarding Study PALO-02-01.
July 9/10, 2003	IND 39,797	Telephone to/from Mr. Brian Strongin	Preliminary reply to FDA's request of July 3, 2003, re pediatric study PALO-99-07 ECG data. FDA receipt of PALO-99-07 ECG data in Sponsor's fax dated July 9, 2003.
July 9/10, 2003	NDA 21-372	Telephone/fax to/from FDA	Clarification of Table 3.8.4:8 regarding QTc values, and associated narrative in Volume 1.1 of the NDA. Schedule for FDA to provide a mark-up of labeling. Reply to Dr.Nair'sECG questions about Volume 1.1, page 220, Table 3.8.4:8 and narrative on that page ot the NDA.
July 11, 2003	IND 39,797	Amendment # 173	Sponsor's reply to FDA request for ECG and related data for pediatric subjects enrolled in PALO-99-07.
July 14, 2003	NDA 21-372	Fax from FDA	Revision to FDA Market-Up Labeling for NDA 21-372 Faxed/E-mailed 7/11/03.
July 17/18, 2003	NDA 21-372	Telephone/Letter to/from FDA	Labeling revisions. Notification to FDA of impending submission of NDA Amendment # 14 and content. FDA schedule for issuance of an FDA decision letter for the NDA. Status of 2330 PK gender analysis. Dr.Nair request for information. Status of NDA 21-372 Amendment # 14. Status of PK data.
July 22, 2003	NDA 21-372	Telephone to/from FDA	Labeling revisions.
July 22, 2003	NDA 21-372	Amendment # 015	Proposed labeling revisions and FDA requested Study 2330 PK data.
July 24, 2003	NDA 21-372	Amendment # 016	Proposed labeling revisions.

July 24, 2003	NDA 21-372	Telephone to/from Mr. Strongin	Labeling revisions.
July 25, 2003	NDA 21-372	Letter from Dr. Beitz/FDA	Approval of NDA 21-372

12. Statement of Eligibility of the Patent for Extension

35 U.S.C. § 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if the following requirements (1)-(5) are satisfied:

(1) the term of the patent has not expired before an application for extension is submitted.

The term of U.S. Patent No. 5,202,333 expires on April 13, 2010. This application has been submitted before the expiration of the patent term. Accordingly, this requirement is satisfied.

(2) the term of the patent has never been extended.

The term of U.S. Patent No. 5,202,333 has never been extended. Accordingly, this requirement is satisfied.

(3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d).

This application is submitted by an agent of the owner of record, Roche Palo Alto LLC. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date that the product received permission for commercial marketing under the Federal Food, Drug, and Cosmetic Act and contains the information required under 35 U.S.C. § 156(d). Accordingly, this requirement is satisfied.

(4) the product has been subject to a regulatory review period before its commercial marketing or use.

As evidenced by the July 25, 2003, letter from FDA, see Attachment H, the product was subject to a regulatory review period under § 505 of the FDCA before its commercial marketing or use. Accordingly, this requirement is satisfied.

(5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

The permission for the commercial marketing and use of palonosetron hydrochloride granted July 25, 2003, after regulatory review by FDA, is the first permitted commercial marketing or use of the product in the United States. Accordingly, this requirement is satisfied.

Because each of these requirements is satisfied, this patent is eligible for an extension.

Statement as to Length of Extension Claimed

The term of U.S. Patent 5,202,333 should be extended by 1827 days, or until April 13, 2015. The length of extension was determined as follows:

As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

(i) the period beginning on the date an exemption under subsection (i) of section 505 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 505.

An Investigational New Drug exemption (IND 39,797) became effective for the product on December 22, 1992. The New Drug Application for the product (NDA 21-372) was submitted on September 27, 2002. Thus, for the purpose of this calculation, period (i) for the product equals the number of days from December 22, 1992, to September 27, 2002, or 3566 days.

(ii) the period beginning on the date the application was initially submitted for the approved product under subsection (b) of section 505 and ending on the date such application was approved under such section.

The NDA for the product was submitted on September 27, 2002. The NDA was approved on July 25, 2003. Thus, for the purpose of this calculation, period (ii) equals the number of days from September 27, 2002 to July 25, 2003, or 301 days.

Under 35 U.S.C. § 156(c), the entire regulatory review period of 3867 days -- the sum of (i) and (ii) above, is reduced by the number of days in the regulatory review period which were on or before the date on which the patent issued. The regulatory review period for the product began on December 22, 1992. U.S. Patent No. 5,202,333 issued on April 13, 1993. The period from December 22, 1992 to April 13, 1993 is 112 days. Therefore, the regulatory review period is calculated as follows: 3867-112= 3755 days.

35. U.S.C. § 156(c) also sets forth the following exceptions (1)-(3) which operate to shorten the length of the review period used to calculate patent term extension:

(1) the review period is reduced by any period during which the applicant did not act with due diligence.

Development was halted for business reasons during the time spanned by the filing of Amendments 051 to 053. See item 11 at page 14. Amendments 050 to 053 were filed, as required. Ownership of the IND was transferred in 1998, as shown in Amendments 054 and 055. At no time did applicant abandon or withdraw the IND or NDA or fail to file required reports, and therefore applicant has not made a deduction in the review period for lack of due diligence.

(2) the review period includes only one-half of the number of days in phase (i) which occurred after the date the patent issued.

Period (i) as calculated above is 3566 days. The number of days between issuance of the patent and initiation of the IND, as calculated above, is 112 days. Therefore, one-half the number of days determined to be in phase (i) after the patent issued is [(3566-112)/2] or 1727 days.

The maximum permissible extension is calculated by adding the 1727 days of period (i) to the 301 days of period (ii), for a total of 2028 days.

(3) if the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

The product was approved on July 25, 2003. US Patent No. 5,202,333 presently is set to expire on April 13, 2010. Thus, the patent term remaining after the date of product approval is the period between July 25, 2003 and April 13, 2010, or 2454 days. When 2454 days is added to the regulatory review period as revised above, 2028 days, the total is 4482 days or 12.5 years, which does not exceed 14 years. Therefore, this limitation does not apply.

35 U.S.C. § 156(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent 5,202,333 is April 13, 2010. Accordingly, the maximum extension allowed by this provision would extend the term to April 13, 2015. Extension of the patent by the number of days calculated above would extend the patent beyond April 13, 2015. Accordingly, pursuant to 35 U.S.C. § 156(g)(6), U.S. Patent 5,202,333 cannot be extended beyond April 13, 2015.

Thus, U.S. Patent No. 5,202,333 is entitled to an extension until April 13, 2015, or 1827 days.

13. Duty of Disclosure

Applicant acknowledges a duty to disclose to the Director of the US Patent & Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought herein.

14. Fees

A check for $1120 (37 CFR 1.20(j)(1)) is enclosed. The Director is hereby authorized to charge any underpayment or credit any overpayment to Deposit Account No. 08-1641, referencing 13265-1163.

15. Name and address for correspondence

Inquiries and correspondence relating to this Application for interim extension of patent term should be directed to:

Customer Number 26633
Heller Ehrman White & McAuliffe, LLP
1666 K Street N.W., Suite 300
Washington DC 20006

Telephone inquiries should be directed to:

John P. Isacson, at (202) 912-2777.

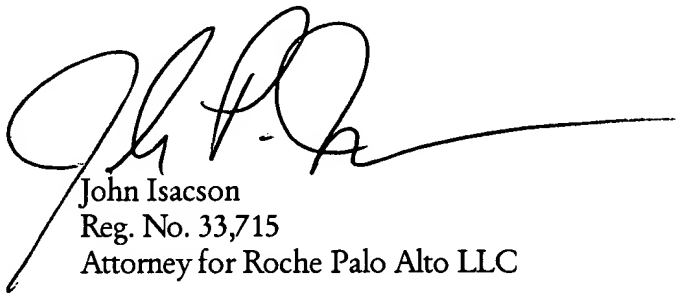
Faxed correspondence should be directed to:

John P. Isacson, at (202) 912-2020.

16. Multiple copies

This Application for extension of patent term is being submitted in an original and two copies. The undersigned hereby certifies that the copies of this Application (together with the appended Attachments A through H) filed herewith are true and correct copies.

Respectfully submitted,



John Isacson
Reg. No. 33,715
Attorney for Roche Palo Alto LLC

Customer No. 26633
Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W.
Suite 300
Washington, D.C. 20006
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

ATTACHMENT A
(Copy of Power of Attorney from Roche Palo Alto LLC
to the practitioners at Customer No. 26633, and executed 3.73 statement)

PTO/SB/81 (06-03)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	07,704,565 (USP 5,202,333)
Filing Date	May 22, 1991
First Named Inventor	Jacob Berger
Title	Tricyclic 5-HT3 Receptor Antagonists
Art Unit	1202
Examiner Name	Mark L. Berch
Attorney Docket Number	13265-1163 (formerly 26890-P1

I hereby appoint:

[X] Practitioners at Customer Number: 26633

OR

[ ] Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

[X] The above-mentioned Customer Number:

OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I am the:

[ ] Applicant/Inventor.

[X] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Name	Nancy M. Cohen VP		
Signature	Nancy M. Cohen		
Date	15 Sept 2003	Telephone	650-855-5217

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of one forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/17 (01-03)
Approved for use through 04/30/2003. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 1,120.00

Complete if Known	
Application Number	5,202,333 (07/704,565)
Filing Date	April 13, 1993 (May 22, 1991)
First Named Inventor	Jacob BERGER et al.
Examiner Name	To be assigned
Art Unit	To be assigned
Attorney Docket No.	13265-1163

METHOD OF PAYMENT (check one)

☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number: 08-1641 (Docket No.)

Deposit Account Name: Heller Ehrman White & McAuliffe LLP

The Commissioner is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		x		=	
Independent Claims		-3** =		x		=	
Multiple Dependent						=	

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	**Reissue independent claims over original patent
1205	18	2205	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify): Patent Term Extension Fee					1,120.00

* Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 1,120.00

SUBMITTED BY				Complete *(if applicable)*
Name *(Print/Type)*	John P. Isaacson	Registration No. *(Attorney/Agent)*	33,715	Telephone (202) 912-2000
Signature		*Date*	September 22, 2003	Customer No. 26633

PATENT
Attorney Docket 26890-P1

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re: US Patent No. 5,202,333

Mailstop PATENT EXTENSION
Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

Sir:

Power of Attorney

Roche Palo Alto LLC states that it is the assignee of the entire interest in US Patent No. 5,202,333 by an assignment from the inventors, Jacob Berger et al., to Syntex (U.S.A.) Inc. recorded on September 13, 1991 at Reel 005829, Frame 0428; the subsequent merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC, for which the Certificate of Merger was recorded on July 9, 2003 at Reel 013782, Frame 0352; and the subsequent change of name of Syntex (U.S.A.) LLC to Roche Palo Alto LLC, for which the Change of Name was recorded on July 10, 2003 at Reel 013782, Frame 0874.

As assignee of the entire interest in US Patent No. 5,202,333, Roche Palo Alto LLC hereby appoints the practitioners at Customer No. 25213 as its attorneys and agents to prosecute applications for interim extension and extension of the patent term of US Patent No. 5,202,333.

Respectfully submitted,
Roche Palo Alto LLC

Nancy M. Cohen
Vice President and Secretary

Date: 16 July 2003

SV 445739 v1
7/16/03 11:34 AM (13265.1163)

PTO/SB/96 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Jacob Berger et al. / Roche Palo Alto LLC

Application No./Patent No.: 07/704,565 / 5,202,333 Filed/Issue Date: May 22, 1991 / April 13, 1993

Entitled: Tricyclic 5-HT3 Antagonists

Roche Palo Alto LLC, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of an undivided part interest

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: Jacob Berger et al. To: Syntex (U.S.A.) Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 005829, Frame 0428, or for which a copy thereof is attached.

2. From: Syntex (U.S.A.) Inc. To: Syntex (U.S.A.) LLC
   The document was recorded in the United States Patent and Trademark Office at Reel 013782, Frame 0352, or for which a copy thereof is attached.

3. From: Syntex (U.S.A.) LLC To: Roche Palo Alto LLC
   The document was recorded in the United States Patent and Trademark Office at Reel 013782, Frame 0874, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☒ Copies of assignments or other documents in the chain of title are attached.

[**NOTE**: A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.8]

The undersigned (whose title is supplied below) is empowered to sign this statement on behalf of the assignee.

15 Sept. 2003
Date

Nancy M. Cohen
Signature

Nancy M. Cohen
Typed or printed name

Attorney for Roche Palo Alto LLC, VP
Title

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE: 12/18/91
TO:
WAYNE W. MONTGOMERY
PATENT DEPT., SYNTEX (U.S.A.) INC.
3401 HILLVIEW AVE.
P.O. BOX 10850
PALO ALTO, CA 94303

CORRECTED NOTICE

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS, ON THIS NOTICE, PLEASE SEND A REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

RECEIVED
DEC 27 1991
SYNTEX PATENT DEPT.
PALO ALTO

ASSIGNOR: DOC DATE: 09/05/91
BERGER, JACOB

ASSIGNOR: DOC DATE: 08/29/91
CLARK, ROBIN D.

ASSIGNOR: DOC DATE: 08/29/91
EGLEN, RICHARD M.

ASSIGNOR: DOC DATE: 08/29/91
SMITH, WILLIAM L.

ASSIGNOR: DOC DATE: 08/29/91
WEINHARDT, KLAUS K.

RECORDATION DATE: 09/13/91 NUMBER OF PAGES 004 REEL/FRAME 5829/0428

DIGEST :ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
SYNTEX (U.S.A.) INC.
A CORPORATION OF DE
P.O. BOX 10850
3401 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94303

RECEIVED
SEP 25 2003
OFFICE OF PETITIONS

SERIAL NUMBER	7-704565	FILING DATE	05/22/91
PATENT PATENT		ISSUE DATE	00/00/00

Form PTO-140
(3-75)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

DEPOSIT ACCOUNT ORDER FORM

BEFORE USING THIS ORDER FORM read the important information on the reverse side

MAIL TO: Commissioner of Patents and Trademarks
Washington, D.C. 20231

Date: Nov. 26, 1991

Account No.: 19-5430

Order No.: 996

Name and Address of Depositor:

PATENT DEPARTMENT A2-200
Syntex (U.S.A.) INC.
3401 Hillview Avenue
Palo Alto, CA 94303

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ITEM OR SERVICE	VALUE FURNISHED ACTION OFF. USE

DESCRIPTION OF ARTICLES OR SERVICES TO BE FURNISHED

Recordal of Serial Number Assignment

Inventor(s): Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt

Assignee: Syntex (U.S.A.) Inc.

Serial No.: 07/704,565

Filing Date: May 22, 1991

Case No.: 26890-CIP

Recordal Fee - $8.00 (37 CRF 1.21(h) (1))

[illegible] 12/13/91 07704565 19-5430 030 518 8.00CH

If additional space is needed attach separate sheet.

Wayne W. Montgomery (Signature) Reg. No. 35,016

FOR PROMPT, ACCURATE SHIPMENT PLEASE COMPLETE THE FOLLOWING MAILING LABEL—PLEASE PRINT OR TYPEWRITE

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
OFFICIAL BUSINESS
RETURN AFTER FIVE DAYS

CASE # 26890-CIP

YOUR ORDER NO.

996

NAME SYNTEX (U.S.A.) INC. - PATENT DEPT. A2-200

STREET ADDRESS 3401 Hillview Avenue P.O. Box 10850

CITY, STATE, ZIP CODE Palo Alto, California 94303

Case 26890-CIP

ASSIGNMENT

WHEREAS, we, Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, of Los Altos Hills, California; Palo Alto, California; Mountain View, California; Sunnyvale, California; and San Francisco, California, respectively, have invented certain new and useful improvements (the "Invention") in

TRICYCLIC 5-HT$_3$ RECEPTOR ANTAGONISTS

which is described in an application for Letters Patent of The United States of America executed by us on September 5, 1991; August 29, 1991; August 29, 1991; August 29, 1991; and August 29, 1991, respectively; and filed in the United States Patent and Trademark Office on May 22, 1991, under Serial No. 07/704,565;

AND WHEREAS, SYNTEX (U.S.A.) INC., a corporation of Delaware, having an address at 3401 Hillview Avenue, P.O. Box 10850, Palo Alto, California 94303, is desirous of acquiring an interest therein and in the Letters Patent to be obtained therefore from the United States;

NOW, THEREFORE, in exchange for good and valuable consideration, the receipt and sufficiency are hereby acknowledged, we, Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, by these presents do hereby assign, sell and transfer unto said SYNTEX (U.S.A.) INC., for the territory of The United States of America and for all foreign countries, the full and exclusive right, title and interest, including all rights under the Paris Convention for the Protection of Industrial Property, in the Invention, as described in the specification of the application for Letters Patent of The United States under Serial No. 07.704,543, or in any continuation, division, reissue, reexamination or extension thereof and any legal equivalent thereof in a country foreign to the United States of America; said Invention, application and Letters Patent to be held and enjoyed by said SYNTEX (U.S.A.) INC., for its own use and behoof, and for the use and behoof of its successors, assigns and legal representatives, to the full end of the term for which said Letters Patent may be granted as fully and entirely as the same would have been held by us had this assignment and sale not been made. This assignment is effective as of May 22, 1991.

IN WITNESS WHEREOF, we, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, have read and understood this Assignment document for the Invention described in the application for Letters Patent of The United States of America, Serial No. 07/704,565, and agree hereto, as indicated by our signatures set forth below.

Signature: Robin D. Clark — Date: 8-29-91
Robin D. Clark

Signature: Richard M Eglen — Date: August 29th 1991
Richard M. Eglen

Signature: William L. Smith — Date: 29 August 1991
William L. Smith

Signature: Klaus K. Weinhardt — Date: 8/29/91
Klaus K. Weinhardt

STATE OF CALIFORNIA }
} ss.
COUNTY OF SANTA CLARA }

On this the 29th day of August, 1991, before me, Jean M. Bruder, the undersigned Notary Public, personally appeared Robin D. Clark, Richard M. Eglen, William L. Smith and Klaus K. Weinhardt.

☐ personally known to me

☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) are subscribed to the within instrument, and acknowledged that they executed it.

WITNESS my hand and official seal.

Jean M. Bruder
Notary Public

OFFICIAL NOTARY SEAL
JEAN M. BRUDER
Notary Public — California
SANTA CLARA COUNTY
My Comm. Expires APR 17 1995

IN WITNESS WHEREOF, I, Jacob Berger, have read and understood this Assignment document for the Invention described in the application for Letters Patent of The United States of America, Serial No. 07/704,565, and agree hereto, as indicated by my signatures set forth below.

Signature: Jacob Berger
Jacob Berger

Date: 9-5-91

STATE OF CALIFORNIA }
} ss.
COUNTY OF SANTA CLARA }

On this the 5th day of Sept., 1991, before me, Jean M. Bruder, the undersigned Notary Public, personally appeared Jacob Berger

☐ personally known to me

☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is subscribed to the within instrument, and acknowledged that he executed it.

WITNESS my hand and official seal.

RECEIVED
PATENT AND TRADEMARK
OFFICE
SEP 13 1991

Jean M. Bruder
Notary Public

OFFICIAL NOTARY SEAL
JEAN M. BRUDER
Notary Public — California
SANTA CLARA COUNTY
My Comm. Expires APR 17 1995

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JULY 10, 2003

PTAS

HELLER EHRMAN WHITE & MCAULIFFE LLP
DEREK P. FREYBERG
MENLO PARK, CA 94025-3506

700035674A

700035674A

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RECORDATION DATE: 07/09/2003

REEL/FRAME: 013782/0352
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SYNTEX (U.S.A.) INC.

DOC DATE: 05/30/2000

ASSIGNEE:
SYNTEX (U.S.A.) LLC
3431 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304

SERIAL NUMBER: 07704565
PATENT NUMBER: 5202333

FILING DATE: 05/22/1991
ISSUE DATE: 04/13/1993

LAZENA MARTIN, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

07/09/2003
700035674

RECORDATION FORM COVERSHEET (PATENTS)

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being transmitted by facsimile to the US PTO at (703) 306-5995 on July 9, 2003.

Derek P. Freyberg, Reg. No. 29,250 — 7/9/03 Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Please record the attached document:

1. Name of conveying party:	Syntex (U.S.A.) Inc.
2. Name and address of receiving party:	Syntex (U.S.A.) LLC 3431 Hillview Avenue Palo Alto CA 94304
3. Nature and date of conveyance:	Merger; signed May 30, 2000
4. Application or patent number:	Patent No. 5,202,333
5. Correspondence address:	Heller Ehrman White & McAuliffe LLP 275 Middlefield Road Menlo Park CA 94025-3506 Tel: 650.324.7000; fax: 650.324.0638
6. Recordation fee and authorization:	Fee $40; charge to Deposit Account No. 08-1641 (ref. 13265-1163)
7. Total number of pages:	4

8. Statement and signature:
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Derek P. Freyberg
Reg. No. 29,250

CH $40.00 081641 5202333

Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park CA 94025-3506
(650) 324-7014
July 9, 2003

SV 444525 v1 Prev SV 372264
07/09/03 10:43 AM

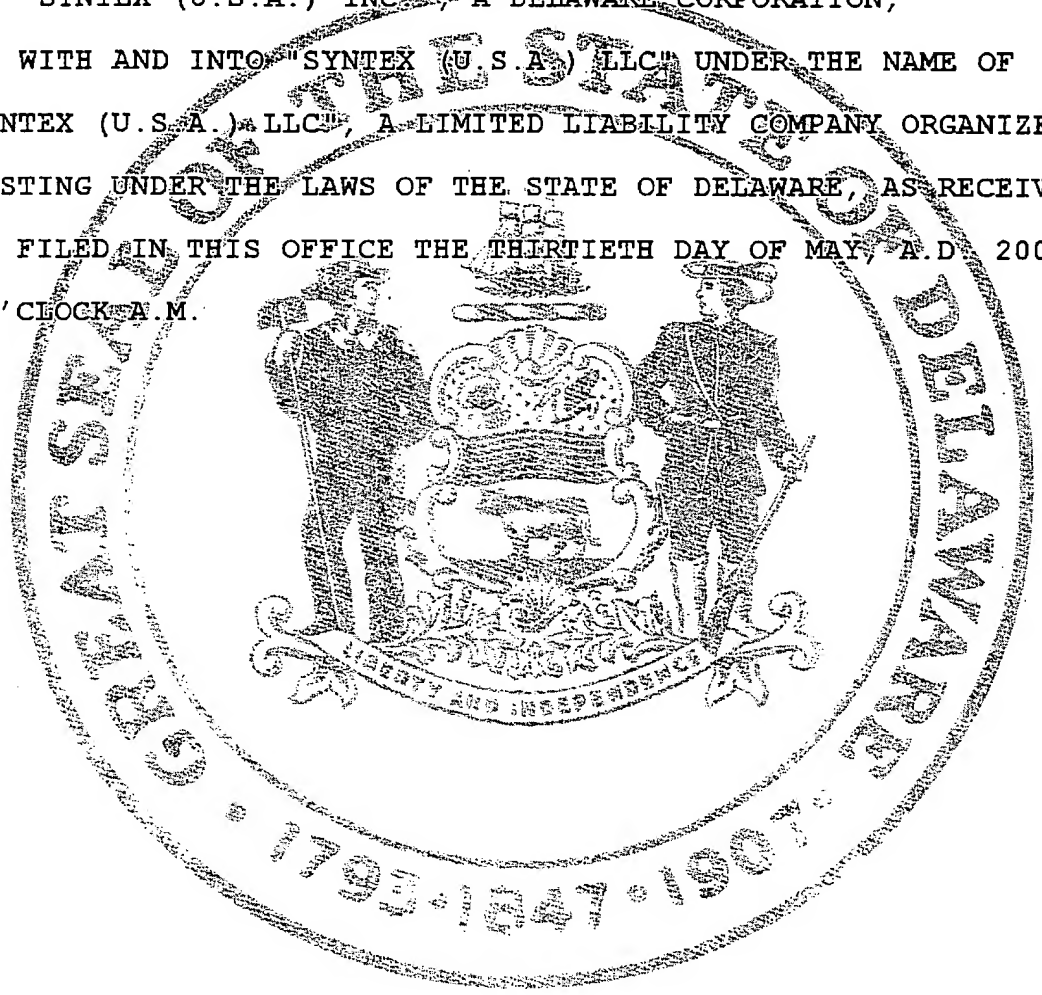
State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"SYNTEX (U.S.A.) INC.", A DELAWARE CORPORATION,

WITH AND INTO "SYNTEX (U.S.A.) LLC" UNDER THE NAME OF "SYNTEX (U.S.A.) LLC", A LIMITED LIABILITY COMPANY ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE THIRTIETH DAY OF MAY, A.D. 2000, AT 9 O'CLOCK A.M.



3205906 8100M

001454182

Edward J. Freel, Secretary of State

AUTHENTICATION: 0664301

DATE: 09-08-00

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 05/30/2000
001271741 - 3205906

CERTIFICATE OF MERGER
OF
SYNTEX (U.S.A.) INC.
INTO
SYNTEX (U.S.A.) LLC

(Under Section 264 of the General Corporation Law of the State of Delaware and Section 18-209 of the Delaware Limited Liability Company Act)

The undersigned limited liability company formed and existing under and by virtue of the Delaware Limited Liability Company Act, 6 Del.C. § 18-101, *et seq.* (the "Act").

DOES HEREBY CERTIFY:

FIRST: The name and jurisdiction of formation or organization of each of the constituent entities which is to merge are as follows:

Name	Jurisdiction of Formation or Organization
Syntex (U.S.A.) Inc.	Delaware
Syntex (U.S.A.) LLC	Delaware

SECOND: An Agreement and Plan of Exchange and Merger has been approved, adopted, certified, executed and acknowledged by each of the constituent entities in accordance with Section 264(c) of the General Corporation Law of the State of Delaware, 8 Del.C. § 191m *et seq.* (the "GCL"), Section 18-209 of the Act and, with respect to Syntex (U.S.A.) Inc., Section 228 of the GCL.

THIRD: The name of the surviving Delaware limited liability company is Syntex (U.S.A.) LLC.

FOURTH: The merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC shall be effective as of the close of business on the day the filing of this Certificate of Merger with the Secretary of State of the State of Delaware is made.

FIFTH: The executed Agreement and Plan of Exchange and Merger is on file at an office of the surviving Delaware limited liability company. The address of such place of business of the surviving Delaware limited liability company is 3401 Hillview Avenue, Palo Alto, California 94304.

SIXTH: A copy of the Agreement and Plan of Exchange and Merger will be furnished by the surviving Delaware limited liability company, on request and without cost, to any member of Syntex (U.S.A.) LLC, and to any stockholder of Syntex (U.S.A.) Inc.

SYNTEX (U.S.A.) LLC

By: _____
Name: Nancy M. Cohen
Title: Vice President & Secretary

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JULY 11, 2003

PTAS

HELLER EHRMAN WHITE & MCAULIFFE LLP
DEREK P. FREYBERG
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

700035848A

700035848A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

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RECORDATION DATE: 07/10/2003

REEL/FRAME: 013782/0874
NUMBER OF PAGES: 3

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SYNTEX (U.S.A.) LLC

DOC DATE: 12/20/2000

ASSIGNEE:
ROCHE PALO ALTO LLC
3431 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304

SERIAL NUMBER: 07704565
PATENT NUMBER: 5202333

FILING DATE: 05/22/1991
ISSUE DATE: 04/13/1993

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

07/10/2003
700035848

RECORDATION FORM COVERSHEET (PATENTS)

CERTIFICATE OF FACSIMILE TRANSMISSION

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Derek P. Freyberg, Reg. No. 29,250 — 7/10/03 Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Please record the attached document:

1. Name of conveying party:	Syntex (U.S.A.) LLC
2. Name and address of receiving party:	Roche Palo Alto LLC 3431 Hillview Avenue Palo Alto CA 94304
3. Nature and date of conveyance:	Change of name; signed December 20, 2000
4. Application or patent number:	Patent No. 5,202,333
5. Correspondence address:	Heller Ehrman White & McAuliffe LLP 275 Middlefield Road Menlo Park CA 94025-3506 Tel: 650.324.7000; fax: 650.324.0638
6. Recordation fee and authorization:	Fee $40; charge to Deposit Account No. 08-1641 (ref. 13265-1163)
7. Total number of pages:	3

8. Statement and signature:
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Derek P. Freyberg
Reg. No. 29,250

CH $40.00 08164I 5202333

Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park CA 94025-3506
(650) 324-7014
July 10, 2003

SV 444762 v1 Prev SV 372264
07/10/03 10:02 AM

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "SYNTEX (U.S.A.) LLC", CHANGING ITS NAME FROM "SYNTEX (U.S.A.) LLC" TO "ROCHE PALO ALTO LLC", FILED IN THIS OFFICE ON THE TWENTY-THIRD DAY OF DECEMBER, A.D. 2002, AT 4 O'CLOCK P.M.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

3205906 8100

020794267

AUTHENTICATION: 2168192

DATE: 12-24-02

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 04:00 PM 12/23/2002
020794267 – 3205906

CERTIFICATE OF AMENDMENT

OF

SYNTEX (U.S.A.) LLC

1. The name of the limited liability company is, upon the effective time of this amendment, Roche Palo Alto LLC.

2. The Certificate of Formation of the limited liability company is hereby amended as follows:

The paragraph labeled "FIRST" is changed to read, The name of the limited liability company formed hereby is Roche Palo Alto LLC.

The heading is changed to read, CERTIFICATE OF FORMATION OF ROCHE PALO ALTO LLC.

3. This Certificate of Amendment shall be effective on 12:01 am, January 1, 2003.

IN WITNESS WHEREOF, the undersigned has executed this Certificate of Amendment of Syntex (U.S.A.) LLC this 20th day of December, 2002.

Nancy M. Cohen
Vice President, Secretary

ATTACHMENT B
(US Patent No. 5,202,333)

US005202333A

United States Patent [19]

Berger et al.

[11] Patent Number: 5,202,333

[45] Date of Patent: Apr. 13, 1993

[54] TRICYCLIC 5-HT$_3$ RECEPTOR ANTAGONISTS

[75] Inventors: Jacob Berger, Los Altos Hills; Robin D. Clark, Palo Alto; Richard M. Eglen, Mountain View; William L. Smith, Sunnyvale; Klaus K. Weinhardt, San Francisco, all of Calif.

[73] Assignee: Syntex (U.S.A.) Inc., Palo Alto, Calif.

[21] Appl. No.: 704,565

[22] Filed: May 22, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 442,082, Nov. 28, 1989, abandoned.

[51] Int. Cl.^{5} C07D 471/08; A61K 31/55; A61K 31/455

[52] U.S. Cl. 514/296; 514/211; 514/872; 540/520; 546/99; 546/100

[58] Field of Search 546/99, 100; 540/520; 514/211, 296

[56] References Cited

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88-04292	6/1988	World Int. Prop. O. .

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1989, Drugs Acting on 5-Hydroxytryptamine Receptors, The Lancet, pp. 717–719.

Scholtysik, G. 1988, 5-Hydroxytryptamine Antagonist ICS 205–930 Blocks Cardiac Potassium, Sodium and Calcium Channels, J. of Pharmacol. Exp. Ther. 245, 3:773–778.

King et al. 1990, Benzotriazinones as "Virtual Ring" Mimics of o-Methoxybenzamides: Novel and Potent 5-HT$_3$ Receptor Antagonists, *J. Med. Chem.* 33:2942–2944.

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Komatsu et al. 1978, Chem. Abs. 89:100352x.

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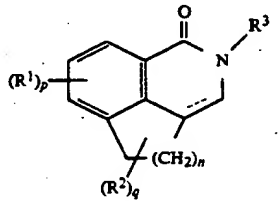
Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Wayne W. Montgomery; Derek P. Freyberg; Tom M. Moran

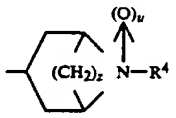
[57] ABSTRACT

The present invention is directed to 5-HT$_3$ receptor antagonist compounds of formula I:

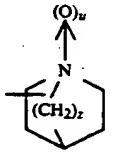


I

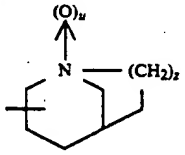
in which
the dashed line denotes an optional double bond;
n is 1, 2 or 3;
p is 0, 1, 2 or 3;
q is 0, 1 or 2;
each R^1 is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;
each R^2 is lower alkyl; and
R^3 is a group selected from Formulae (a), (b), (c) and (d):



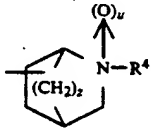
(a)



(b)



(c)



(d)

in which
u is 0 or 1;
z is 1, 2 or 3; and
R^4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR^5$ where t is 1 or 2 and R^5 is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy; and the pharmaceutically acceptable salts, individual isomers, mixtures of isomers, processes for preparation, compositions, and methods of use thereof.

50 Claims, No Drawings

TRICYCLIC 5-HT$_3$ RECEPTOR ANTAGONISTS

This application is a continuation-in-part of copending application, Ser. No. 07/442,082, filed Nov. 28, 1989 and now abandoned.

FIELD OF THE INVENTION

This invention relates to novel compounds which are 5-HT$_3$ receptor antagonists, pharmaceutical compositions containing them and methods for their use and methods for preparing these compounds. In particular, it relates to tricyclic 5-HT$_3$ receptor antagonists containing a bridged bicyclic amine substituent. The invention also relates to novel intermediates for making the 5-HT$_3$ receptor antagonists.

BACKGROUND OF THE INVENTION

Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of substantial research. Serotonin, also referred to as 5-hydroxytryptamine (5-HT), acts both centrally and peripherally on discrete 5-HT receptors. 5-HT Receptors are presently delineated into three major subclassifications - 5-HT$_1$, 5-HT$_2$ and 5-HT$_3$ - each of which may also be heterogeneous. Receptors of the 5-HT$_3$ subclass pervade autonomic neurons and appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.

5-HT$_3$ receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT$_3$ receptor level, i.e., 5-HT$_3$ receptor antagonists, possess potent antiemetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy (see Drugs Acting on 5-Hydroxytryptamine Receptors: *The Lancet* Sep. 23, 1989 and refs. cited therein).

Functional bowel disorders are prevalent in much of the industrialized world. Chronic gastroesophageal reflux disease alone may be present in as much as 15% of the population. Use of prokinetic agents is one of the most effective methods known for treating such disorders. Because many 5-HT$_3$ antagonists possess prokinetic properties and are relatively free from side effects they are particularly useful in the treatment of gastrointestinal diseases (see Reynolds R. C. Prokinetic Agents: A Key in the Future of Gastroenterology. *Gastroenterology Clinics of North America* 1989, 18, 437–457).

5-HT$_3$ receptors are present in those areas of the brain which control mood, emotion, reward and memory. 5-HT$_3$ receptor antagonists reduce mesolimbic dopamine levels, a necessary property for antipsychotic activity. Such antagonists also increase cholinergic tone in the limbic-cortical region, which may explain their cognitive enhancing effects. In addition, 5-HT$_3$ antagonists possess anxiolytic properties, demonstrate potential for use in the treatment of dependency disorders and are under investigation in patients with schizophrenia (see article from *The Lancet* previously cited).

There is evidence that 5-HT$_3$ receptors mediate nociceptive input to afferent neurons (see Glaum, S.; Proudfit, H. K.; Anderson, E. G. *Neurosci. Lett.* 1988, 95, 313). 5-HT$_3$ antagonists may therefore be of value in the control of pain, particularly migraine (see Peatfield R.;

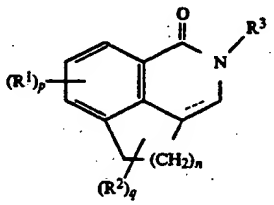
Drugs and the Treatment of Migraine. *Trends. Pharmacol. Sci.* 1988, 9, 141).

The 5-HT$_3$ receptor antagonist ICS 205-930 inhibits arrhythmias in a variety of animal models and exerts mixed class III and class I antiarrhythmic properties in ventricular myocytes (see Scholtysik, G.; Imoto, Y.; Yatani, A; Brown, A. M. *J. Pharmacol. Exp. Ther.* 1988, 245, 773 and references therein). 5-HT$_3$ antagonists may therefore be of use in treating or preventing arrhythmias.

The disclosures of these and other documents referred to throughout this application, e.g., in the Pharmacology section of the Detailed Description of the Invention, are incorporated herein by reference.

SUMMARY OF THE INVENTION

The first aspect of this invention is the compounds of Formula I:



I

in which

the dashed line denotes an optional double bond;

n is 1, 2 or 3;

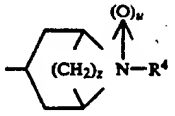
p is 0, 1, 2 or 3;

q is 0, 1 or 2;

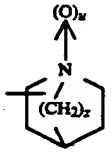
each R^1 is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

each R^2 is lower alkyl; and

R^3 is a group selected from Formulae (a), (b), (c) and (d):



(a)



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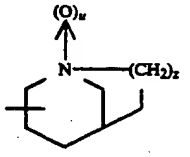

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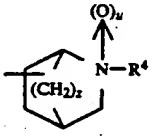


(d)

in which

u is 0 or 1;

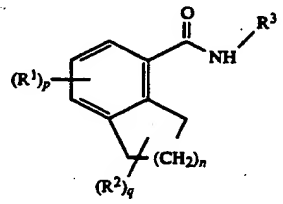
z is 1, 2 or 3; and

R^4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR^5$ where t is 1 or 2 and R^5 is thienyl, pyrrolyl, or furyl, each optionally substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl optionally further substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy; and the pharmaceutically acceptable salts, individual isomers and mixtures of isomers thereof.

A second aspect of this invention is a pharmaceutical composition containing a compound of Formula I in admixture with one or more suitable excipients.

A third aspect of this invention is a method of treating diseases involving emesis, gastrointestinal disorders, CNS disorders, cardiovascular disorders or pain by administering a therapeutically effective amount of a compound of Formula I to a subject afflicted with such a condition.

A fourth aspect of this invention is the compounds of Formula II:



II

in which n, p, q, R^1, R^2 and R^3 are as defined for Formula I, which are useful intermediates in preparing compounds of Formula I.

A fifth aspect of this invention are the processes for preparing compounds of Formula I and is set forth in the "Detailed Description Of The Invention."

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a straight, branched, or cyclic saturated hydrocarbon radical having from one to the number of carbon atoms designated. For example C_{1-7} alkyl is alkyl having at least one but no more than seven carbon atoms, e.g., methyl, ethyl, i-propyl, n-propyl, n-butyl, cyclopropylmethyl, pentyl, cyclohexyl, heptyl and the like.

"Alkoxy" means the radical —OR wherein R is alkyl having from one to the number of carbon atoms designated, e.g., C_{1-7} alkoxy includes, e.g., methoxy, ethoxy, i-propoxy, n-propoxy, n-butoxy, pentoxy, hexoxy and the like.

"Alkonyl" means the radical —C(O)R wherein R is alkyl having from one to the number of carbon atoms designated, e.g., C_{1-7} alkonyl includes ethanoyl, propanoyl, i-butanoyl, n-butanoyl, pentanoyl, hexanoyl and the like.

"Lower" modifies alkyl, alkoxy and alkonyl and refers to those alkyl radicals or R groups in alkoxy and alkonyl radicals containing 1 to 6 carbon atoms.

"Halogen" means fluorine, chlorine, bromine, or iodine.

"Esterified carboxy" means the ester group —COOR wherein R is C_{1-8} alkyl.

"In vivo hydrolyzable acyloxy" means a group —OC(O)R, wherein R is C_{1-8} alkyl, capable of undergoing enzymatic hydrolysis within a living organism.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes halogen and alkane- or arenesulfonyloxy such as mesyloxy, ethanesulfonyloxy, benzenesulfonyloxy, tosyloxy and the like.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals (e.g., birds and the like).

"Cytotoxic agents" include platinum anti-cancer agents such as cisplatin (cis-diamminedichloroplatinum), as well as non-platinum anti-cancer drugs such as cyclophosphamide (cytoxin), vincristrine (leurocristine), procarbazine (N-(1-methylethyl)-4-[(2-methylhydrazino)methyl]benzamide), methotrexate, fluorouracil, mechlorethamine hydrochloride (2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride), doxorubicin, adriamycin, dactinomycin (actinomycin-D) cytarabine, carmustine, dacarbazine, and others listed at page 1143 of the *Journal of Clinical Oncology* 1989; 7(8): 1143.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy. Thus, "disease" here includes the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with cytotoxic agents and radiotherapy.

"Emesis", for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present and that the description includes both single bonds and double bonds; "optionally converting a compound of Formula I to a corresponding pharmaceutically acceptable salt" means that the conversion may or may not be carried out in order for the process described to fall within the invention, and the invention includes those processes wherein the compound of Formula I is converted to the salt and those processes in which it is not.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological

activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.-2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting its development, or

(3) relieving the disease, i.e., causing regression of the disease.

Compounds that have identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed "isomers". Isomers that differ in the nature or sequence of bonding of their atoms are termed "constitutional isomers". Isomers that differ only in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diasteromers" and stereoisomers that are mirror images are termed "enantiomers" or sometimes "optical isomers". Stereoisomers that are superimposable upon their mirror images are termed "achiral" and those not superimposable are termed "chrial". A carbon atom bonded to four different groups is termed a "chiral center" or alternatively an "asymmetric carbon".

When a compound has a chiral center, a pair of enantiomers of opposite chirality is possible. An enantiomer can be characterized by the absolute configuration of its chiral center and described by the R- and S-sequencing rules of Cahn and Prelog (i.e., as (R)- and (S)-isomers) or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- and (−)-isomers, respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a "racemic mixture" or "racemate" and may be described as the (RS)- or (±)-mixture thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 3rd edition March, Jerry, John Wiley and Sons, New York, 1985).

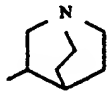
Certain compounds of Formulae I and II can exist as stereoisomers. For example, certain compounds possess a chiral center at the ring carbon of the R^3 substituent which is bonded to the amide nitrogen and, when the optional bond is absent, at the 3a-position and therefore can exist as (R)- or (S)-isomers. In addition, certain compounds can exist as the (endo)- or (exo)-isomers, e.g., when the R^3 substituent is 1-azabicyclo[3.3.1]non-4-yl.

When a compound of Formula I or II possesses one chiral center, a pair of enantiomers exists. When two chiral centers are present in a compound of Formula I, four separate steroisomers exist (i.e., two separate pairs of enantiomers). When a compound of Formula I possesses two chiral centers and can exist as endo or exo, eight separate stereoisomers are possible (i.e., two separate pairs of enantiomers in the endo or exo form).

It is to be understood that when referring to Formula I, II, (a), (b), (c) or (d) in this application, a straight line depicting the covalent bond between the R^3 substituent and the amide nitrogen represents the possible geometric isomers and enantiomers or the mixtures, racemic or otherwise, thereof. Similarly, when referring to Formula I in which the optionally bond is absent, a straight line depicting the covalent bond between carbons 3a and 4 represents either the R or S configurations or a mixture racemic, or otherwise, thereof. For purposes of the present application when referring to a compound by name or by formula and the configuration is not designated, it is to be understood that the reference is to all possible forms.

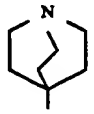
Certain R^3 substituents described in this application are of particular interest and are therefore defined specifically as the following:

(1) Formula (b) where z is 2 and u is 0 having the specific formula



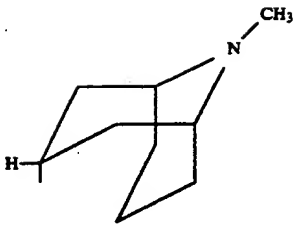
is referred to as 1-azabicyclo[2.2.2]oct-3-yl;

(2) Formula (b) where z is 2 and u is 0 having the specific formula



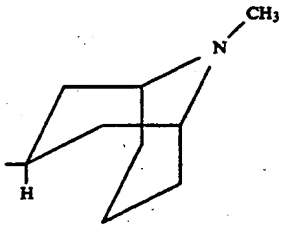
is referred to as 1-azabicyclo[2.2.2]oct-4yl;

(3) Formula (a) where z is 3, u is 0 and R^4 is methyl having the specific formula



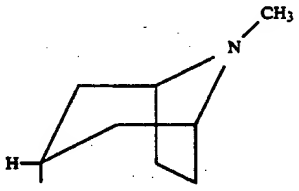
is referred to as (endo)-9-methyl-9-azabicyclo[3.3.1]-non-3-yl;

(4) Formula (a) where z is 3, u is 0 and R^4 is methyl having the specific formula



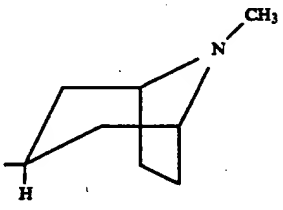
is referred to as (exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl;

(5) Formula (a) where z is 2, u is 0 and R^4 is methyl having the specific formula



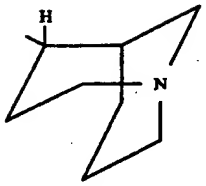
is refered to as (endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;

(6) Formula (a) where z is 2 u is 0 and R^4 is methyl having the specific formula



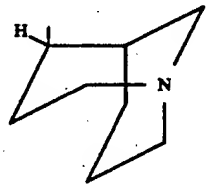
is referred to as (exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;

(7) Formula (c) wherein z is 2 and u is 0 having the specific formula



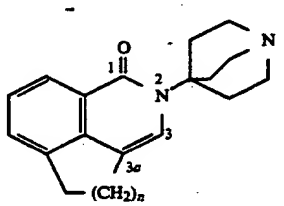
is referred to as (endo)-1-azabicyclo[3.3.1]non-4-yl.

(8) Formula (c) wherein z is 2 and u is 0 having the specific formula



is referred to as (exo)-1-azabicyclo[3.3.1]non-4-yl.

Compounds of Formulae I and II are named in accordance with generally acceptable nomenclature rules established by "Chemical Abstracts." For example, the compound of Formula I in which the optional bond is present, p, q and u are 0 and R^3 is 1-azabicyclo-[2.2.2]oct-4-yl:



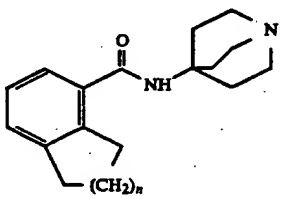
is named

2-(1-azabicyclo[2.2.2]oct-4-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one when n is 1;

2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one when n is 2; and

2-(azabiyclo[2.2.2]oct-4-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one when n is 3.

The compound of Formula II in which the optional bond is present, p, q and u are 0 and R^3 is 1-azabicyclo-[2.2.2]oct-4-yl:



is named

N-(1-azabioyclo[2.2.2]oct-4-yl)-4-indancarboxamide when n is 1;

N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide when n is 2; and

N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide when n is 3.

PRESENTLY PREFERRED EMBODIMENTS

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formulae I and II are preferred. For example, preferred compounds of Formula I are those in which both q and u are 0, p is 1, or 2, each R^1 is independently selected from halogen, lower alkoxy or amino, and R^4 is lower alkyl.

Of particular interest are those compounds of Formula I in which each p, q and u are 0, R^4 is methyl, and R^3 is one of the following groups:
1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo-[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
endo-1-azabicyclo[3.3.1]non-4-yl; or
exo-1-azabicyclo[3.3.1]non-4-yl.

Of most interest are the compounds of Formula I in which each p, q and u are 0, and R^3 is 1-azabicyclo[2.2.-2]oct-3-yl, in particular wherein one or, when present, both chiral centers possess S configurations.

Preferred compounds of Formula II are those in which both p and q are 0, p is 0, 1, or 2, each R^1 is independently selected from halogen, lower alkoxy or amino, and R^4 is lower alkyl.

Of particular interest are those compounds of Formula II in which each p, q, and u are 0, R^4 is methyl, and R^3 is one of the following groups:
1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo-[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
endo-1-azabicyclo[3.3.1]non-4-yl; or
exo-1-azabicyclo[3.3.1]non-4-yl.

Of most interest are compounds of Formula II in which each p, q, and u are 0, and R^3 is 1-azabicyclo[2.2.-2]oct-3-yl, in particular the S-isomers thereof.

It is understood that these compounds of Formula II of special interest are particularly useful in the synthesis of preferred compounds of Formula I.

UTILITY

Compounds of Formula I exhibit utility in treating a broad range of diseases in animals, particularly humans. Examples of diseases that may be treated using the compounds of Formula I include emesis, gastrointestinal disorders, central nervous system (CNS) disorders, cardiovascular disorders or pain.

Compounds of Formula I are useful in the prevention and treatment of emesis. Causes of such emesis include surgical anesthesia, psychological stress, pregnancy, certain disease states, radiotherapy, radiation poisoning and toxic substances. Disease states which are known to induce emesis include conditions such as gut obstruction, raised intracranial pressure, acute myocardial infarction, migraine headaches and adrenal crisis. Toxic substances which induce emesis include toxins in the form of abnormal metabolites or abnormal accumulation of natural occurring substances associated with such conditions as hepatic coma, renal failure, diabetic ketoacidosis, hyperthyroid crisis, both hypo- and hyperparathyroidism and Addison's disease. Emesis may also be caused by ingested toxins, e.g., enterotoxins in staphylococcus-contaminated foods, or by drugs administered for therapeutic purposes, e.g., digitalis, emetine and chemotherapeutic agents.

Compounds of Formula I are of particular value in treating (especially preventing) the emesis induced by radiation poisoning, treatment for cancer with radiotherapy or chemotherapy with cytotoxic agents or drug therapy in general wherein a significant side effect is emesis, e.g., amphotericin B in treating immunosuppressed patients, zidovudine (AZT) in the treatment of AIDS and interleukin in treating cancer.

Compounds of Formula I are useful as prokinetic agents in the treatment of gastrointestinal diseases, i.e., diseases of the stomach, esophagus and of both the large and small intestines. Examples of specific diseases include, but are not limited to, dyspepsia (e.g., non-ulcer dyspepsia), gastric stasis, peptic ulcer, reflux esophagitis, flatulence, bile reflux gastritis, pseudo-obstruction syndrome, irritable colon syndrome (which may result in chronic constipation and diarrhea), diverticular disease, biliary dysmotility (which may result in sphincter of Oddi dysfunction and "sludge" or microscopic crystals in the gall bladder), gastroparesis (e.g., diabetic, postsurgical or idiopathic), irritable bowel syndrome amd retarded gastric emptying. The compounds of Formula I are also useful as short-term prokinetics to facilitate diagnostic radiology and intestinal intubation. In addition, the compounds are useful for treating diarrhea, particularly diarrhea induced by cholera and carcinoid syndrome.

Compounds of Formula I are useful in treating diseases of the central nervous system. Categories of such diseases include cognitive disorders, psychoses, obsessive/compulsive and anxiety/depression behavior. Cognitive disorders include attentional or memory deficit, dementia states (including senile dementia of the Alzheimer's type and aging), cerebral vascular deficiency and Parkinson's disease. Psychoses that are treatable using the compounds of Formula I include paranoia, schizophrenia and autism. Obsessive/compulsive behavior that is treatable using compounds of Formula I includes eating disorders, e.g., bulimia, a condition in which an abnormal and constant craving for food is present.

Representative, treatable anxiety/depressive states include anticipatory anxiety (e.g., prior to surgery, dental work, etc.), depression, mania, seasonal affective disorder (SAD), and the convulsions and anxiety caused by withdrawal from addictive substances such as opiates, benzodiazapines, nicotine, alcohol, cocaine and other drugs of abuse.

Compounds of Formula I are useful in the treatment of cardiovascular diseases. Such diseases include arrhythmias and hypertension.

It is thought that 5-HT_3 antagonists prevent certain adverse nervous transmissions and/or prevent vasodilation and are therefore of value for reducing perceived levels of pain. Compounds of Formula I are, therefore, useful in treating pain such as that associated with cluster headaches, migraines, trigeminal neuralgia and visceral pain (e.g., that caused by abnormal distension of hollow visceral organs).

In summary, an aspect of this invention is a method for treating an animal, particularly a human, exhibiting a disease involving emesis, a gastrointestinal disorder, a CNS disorders, a cardiovascular disorder or pain by

administering a therapeutically effective amount of a compound of Formula I to such animal.

Pharmacology

5-HT_3 Receptor binding affinity is measured at 5-HT_3 receptors in membranes prepared from the cerebral cortex of rat brains, an accepted in vitro assay (e.g., see Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. *Nature* 1987, 330, 24–31). The 5-HT_3 receptor binding assay is described in Example 14. The compounds of Formula I exhibit affinity for the 5-HT_3 receptor in this assay.

5-HT_3 receptor antagonist activity is measured by the ability of compounds to inhibit the von Bezold-Jarisch reflex in anesthetized rats, an accepted in vivo assay (e.g., see Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C. C.; Tylers, M. B. *Brit. J. Pharmacol.* 1988, 94, 397–412; Cohen, M. L.; Bloomquist, W.; Gidda, J. S.; Lacefield, W. *J. Pharmacol. Exp. Ther.* 1989; 248, 197–201; Fozard, J. R. *Arch. Pharmacol.* 1984, 326, 36–44). The 5-HT_3 receptor antagonist assay is described in Example 15.

Anti-emetic activity is determined by measuring reduction of cisplatin-induced emesis in ferrets, an accepted assay (e.g., Costall, B.; Domeney, A. M.; Naylor, R. J.; Tattersall, F. D. *Neuropharmacology* 1986, 25(8), 959–961; Miner, W. D.; Sanger G. J. *Brit. J. Pharmacol.* 1986, 88, 497–499). The ferret, anti-emetic assay is described in Example 16.

Anti-emetic activity is also determined by measuring reduction of cisplatin-induced emesis in dogs, an accepted assay (e.g., see Smith, W. L.; Alphin, R. S.; Jackson, C. B.; Sancilio, L. F. *J. Pharm. Pharmacol.* 1989, 41, 101–105; Gylys, J. A. *Res. Commun. Chem. Pathol. Pharmacol.* 1979, 23(1), 61–68). The dog, anti-emetic assay is described in Example 17.

Prokinetic activity is determined by measuring the rate of gastric emptying after oral administration of test meal to rats, an accepted in vivo assay (e.g., see Droppleman, D.; Gregory, R.; Alphin, R. S. *J. Pharmacol. Methods* 1980, 4(3), 227–30). The prokinetic assay is described in Example 18.

Anxiolytic activity is determined by the art-recognized Crawley and Goodwin two-compartment exploratory model (e.g., see Kilfoil, T.; Michel, A.; Montgomery, D.; Whiting, R. L.; *Neuropharmacology* 1989, 28(9), 901–905). In brief, the method involves determining whether a compound reduces the natural anxiety of mice in a novel, brightly lighted area. The anxiolytic behavior assay is described in Example 19.

Anxiolytic activity during withdrawal from drugs of abuse is determined by the mouse, withdrawal anxiety test, an accepted assay (e.g., see Carboni, E.;, Acquas, E.; Leone, P.; Perezzani, L.; Di Chiara, G. *Eur. J. Pharmacol* 1988, 151, 159–160). This procedure utilizes the exploratory model described above to test for anxiolytic activity after chronic administration and subsequent abrupt cessation of ethanol, diazepam, cocaine or nicotine treatments. The withdrawal anxiety assay is described in Example 20.

Cognition enhancing activity is determined by the mouse, habituation/cognitive enhancement test (e.g., see Barnes, J. M.; Costall, B.; Kelly, M. E.; Naylor, F. J.; Onaivi, E. S.; Tomkins, D. M.; Tyers, M. B. *Br. J. Pharmacol.* 1989, 98, 693P). This procedure utilizes the exploratory model described above to test for improvements in the impaired cognitive performance of aged mice. The cognitive enhancement assay is described in Example 21.

Administration and Pharmaceutical Composition

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another compound of Formula I or with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. Therapeutically effective amounts of compounds of Formula I may range from approximately 1.0 nanogram per Kg (ng/Kg) body weight per day to 1.0 mg/Kg body weight per day. Preferably the amount will be approximately 10 ng/Kg/day to 0.1 mg/Kg/day. Therefore, a therapeutically effective amount for a 70 Kg human may range from 70 ng/day to 70 mg/day, preferably 700 ng/day to 7.0 mg/day.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease.

In general, compounds of Formula I will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula I. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

Compressed gases may be used to disperse the compound of Formula I in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, nitrous oxide, etc. Other suitable pharmaceutical carriers and their formulations are described in A. R. Alfonso 1985. Reminton's Pharmaceutical Sciences. 17th ed. Easton, Pa.: Mack Publishing Company.

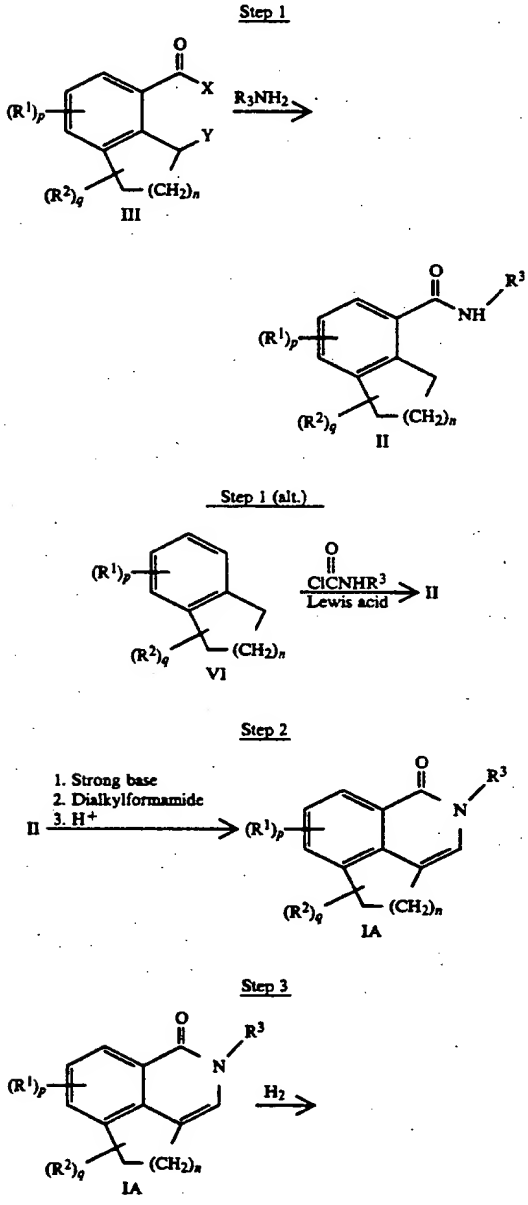
The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, the final composition will comprise from 0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w, with the remainder being the excipient or excipients.

Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 13.

Processes for Preparing Compounds of the Invention

Compounds of Formula I are prepared by the reaction sequence shown below in Reaction Scheme I.

SCHEME I



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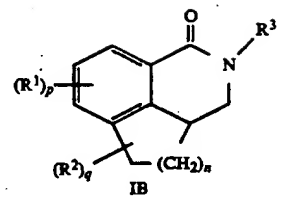
SCHEME I



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in which X is hydroxy, alkoxy or halogen and Y is hydrogen or X and Y together are oxa, and n, p, q, R^1, R^2 and R^3 are as defined in the Summary of the Invention with the processes applying particularly well to the presently preferred embodiments.

Scheme I

Compounds of Formula I are conveniently prepared by a two step synthesis comprising (1) converting an acid or acid derivative of Formula III or a fused-ring bicyclic compound of Formula VI to a substituted amide of Formula II and (2) reacting the amide with a formylating agent in the presence of a strong base and then acidifying to form a compound of Formula IA (a compound of Formula I in which the optional bond is present). Compounds of Formula IB (compounds of Formula I in which the optional bond is absent) are subsequently prepared by reduction.

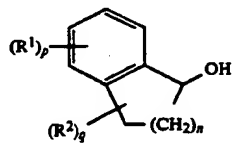
Step 1

Compounds of Formula II are prepared by reacting a compound of Formula III with a substituted amine of the formula NH_2R^3 in which R^3 is as defined in the Summary of the Invention. Reaction conditions are those standard for amide formation (e.g., see *J. Advanced Organic Synthesis* March 1985, 3rd Ed., 370-376). Generally the reaction is carried out at 20° C. to 200° C., preferably −10° C. to 20° C., and ambient pressure for 0.5 to 3 hours in a suitable inert organic solvent (e.g., methylene chloride, THF and toluene). The conversion of a compound of Formula III in which X is ethoxy to the corresponding amide of Formula II is described in Example 2. The conversion of a compound of Formula III in which X is hydroxy to the corresponding amide of Formula II is described in Example 3. The conversion of a compound of Formula III in which X and Y together are oxo to the corresponding amide of Formula II is described in Example 5.

Alternatively, compounds of Formula II may be prepared by Friedel-Crafts acylation in which a chloroformamide of the formula $ClC(O)NHR^2$ is reacted with a compound of Formula VI in the presence of a Lewis acid such as aluminum chloride, boron trifluoride, hydrogen fluoride or phosphoric acid.

In general, the starting materials utilized in the preparation of compounds of Formula II are known to or can readily be synthesized by those of ordinary skill in the art. For example, the compounds of Formula III where X is hydroxy, p is 1, R^1 is methoxy (particularly meta to the acid), q is 0 and n is 1 or 2 are discussed by Lowenthal, H. J.; Schatzmiller, S. *J. Chem. Soc. Perkin Trans. I* 1976, 944. Unsubstituted compounds (i.e., wherein p and q are both 0) in which n is 1, 2 or 3 are readily available or may be prepared in accordance with methods known in the art.

Compounds of Formula III wherein X and Y are together oxa and n is 1, 2 or 3 can be prepared from an alcohol of the formula



in which n, p, q, R^1 and R^2 are as defined in the Summary of the Invention by treating with a strong base (e.g., n-butyllithium) in an inert organic solvent (e.g., hexanes) for approximately 20 hours followed by bubbling through with carbon dioxide for approximately 5 hours. The preparation of a compound of Formula III in which X and Y together are oxa is described in Example 1.

Other starting materials that are useful for preparing compounds of the invention are 1-cyano-4-alkoxynaphthalenes which can be hydrolyzed and reduced to the corresponding starting acid of Formula III wherein X is hydroxy, R is 4-alkoxy, q is 0 and n is 2. Halogen-substituted tetralones are well known and are prepared from o-halophenylbutyric acids. These tetralones can be reduced to the appropriate alcohol, converted to an acid and reacted with the R^3NH_2 compound as a lactone to form an amide of Formula II.

Step 2

Compounds of Formula IA are prepared by reacting amides of Formula II with a dialkylformamide in the presence of a strong base and than acidifying. The reaction is carried out in a inert ethereal solvent (e.g., diethyl ether, dimethoxyethane or tetrahydrofuran (THF), preferably THF) at temperatures ranging from −70° C. to 25° C., preferably −20° C. to 0° C., at ambient pressure and under an inert atmosphere (e.g., argon or nitrogen, preferably nitrogen). The dialkylformamide, preferably dimethylformamide (DMF), is generally used in molar excess relative to the amide of Formula II. Any strong base, such as a Grignard reagent or an appropriate alkyllithium, preferably n-butyllithium, can be utilized. Step 2 of Scheme I is described in Examples 6, 7, 8 and 9.

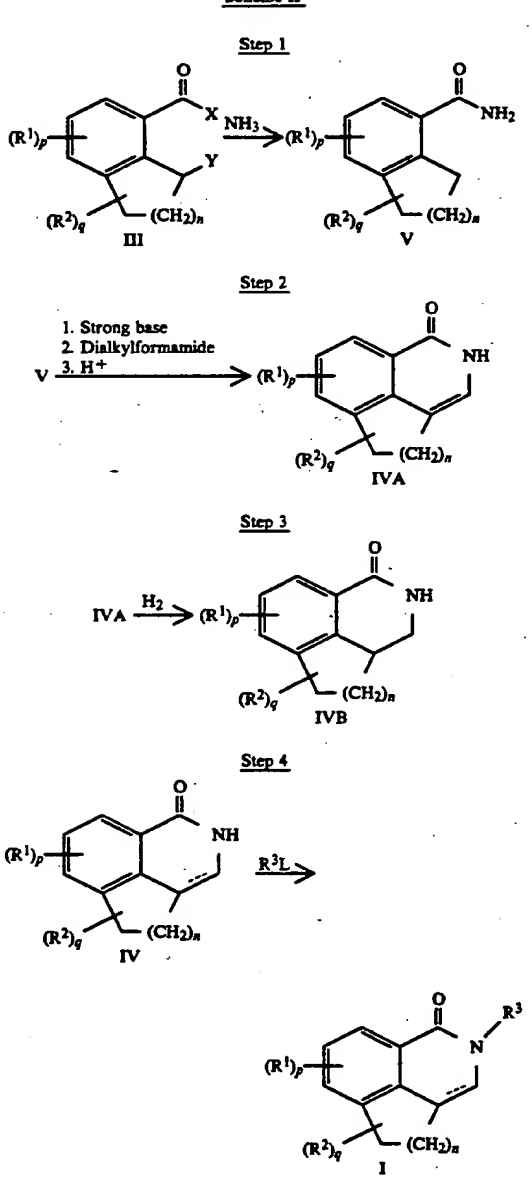
Compounds of Formula IB may be prepared by reduction of the corresponding compound of Formula IA. The reduction is carried out under standard hydrogenation conditions with an appropriate hydrogenation catalyst and in a suitable polar, organic solvent. Reaction pressures may vary from atmospheric to approximately 15 megaPascals (mPa) and temperatures may range from ambient to approximately 100° C. While any standard catalyst (e.g., rhodium on alumina, etc.) may be used, certain catalysts are preferred. Preferred catalysts include 10% palladium hydroxide, 20% palladium hydroxide on carbon, Pearlman's catalyst (50% H_2O−20% palladium content) and palladium/$BaSO_4$. Suitable solvents include ethanol, DMF, acetic acid, ethyl acetate, tetrahydrofuran, toluene, and the like.

Depending upon the catalyst, solvent, pressure and temperature chosen, the reduction process may take from a few hours to a few days to complete. As an example, a reaction carried out with 20% palladium hydroxide in acetic acid and 70% perchloric acid at 15 kPa and 85° C. takes approximately 24 hours for full reduction to occur. The reduction of a compound of Formula IA to a compound of Formula IB is described in detail in Example 10.

A compound of Formula IA can be reduced in either the nonsalt or salt form. If an optically active reagent is employed to form the salt of a compound of Formula IA, formation of one enantiomer over the other may be favored.

Compounds of Formula I are also prepared by the reaction sequence shown below in Scheme II.

Scheme II



in which X is hydroxy, alkoxy or halogen and Y is hydrogen or X and Y together are oxa, L is a leaving group and n, p, q, R^1, R^2 and R^3 are as defined in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

Scheme II

Alternatively, compounds of Formula I are prepared by a three step synthesis comprising (1) converting an acid or acid derivative of Formula III to an unsubstituted amide of Formula V, (2) reacting the amide with a formylating agent in the presence of a strong base and then acidifying to form a compound Formula IVA (a compound of Formula IV in which the optional bond is present), (3) optionally reducing a compound of Formula IVA to a compound of Formula IVB (a compound of Formula IV in which the optional bond is absent) and (4) condensing the compound of Formula IV with an appropriate alkylating agent to form a compound of Formula I.

Step 1

Compounds of Formula V are prepared by proceeding as in Step 1 of Scheme I but replacing the substituted amine with ammonia.

Step 2

Compounds of Formula IVA are prepared by proceeding as in Step 2 of Scheme I but substituting a compound of Formula V for the compound of Formula II. Compounds of Formula IVB may be prepared by proceeding as described above for the hydrogenation of a compound of Formula IA but substituting a compound of Formula IVA.

Step 3

Compounds of Formula I are prepared by reacting, in the presence of a strong base, a compound of Formula IV with an alkylating agent of the formula R^3L in which R^3 is as defined in the Summary of the Invention and L is a leaving group. The reaction is carried out under standard amide alkylating conditions (Luh, T.; Fung S. H. *Synth. Commun.* 1979, 9, 757) in an inert solvent at a reaction temperature of 20° C. to 100° C. Appropriate bases include sodium or sodium hydride and are usually employed in molar excess. Suitable solvents include tetrahydrofuran or N,N-dialkylformamides such as N,N-dimethylformamide.

Alternatively, alkylation may be accomplished via phase-transfer catalyst (PTC) techniques. Such techniques comprise carrying out the reaction in the presence of catalyst and in a liquid-liquid two phase solvent system (Gajda, T.; Zwierzak, A. *Synthesis, Communications* 1981, 1005), or preferably, in a solid-liquid system (Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* 1981, 1143; Koziara, A.; ZaWasZki, S; Zwierzak, A. *Synthesis* 1979, 527, 549).

A liquid-liquid two-phase system is comprised of an aqueous phase consisting of a concentrated alkali hydroxide solution (e.g., 50% aqueous sodium hydroxide), an organic phase comprised of an inert water-immiscible organic solvent solvent, and an appropriate catalyst. A solid-liquid system consists of a powdered alkali hydroxide/alkali carbonate suspended in an organic solvent and catalyst.

The reaction is effected by adding slowly to a PTC system containing a compound of Formula IV an alkylating agent of the formula R^3L until 10 to 50% in excess. The reaction mixture is kept at reflux until the reaction is complete. The mixture is then cooled to room temperature and the compound of Formula I is isolated by conventional methods. Suitable organic solvents include benzene, toluene, and the like. Appropriate catalysts include alumina coated with potassium fluoride and quaternary ammonium sulfates such as tetra-n-butyl-ammonium hydrogen sulfate and tricaprylylmethylammonium chloride.

A variation of Scheme II comprises converting a compound of Formula V to a compound of Formula II by one of the above described alkylation processes and then proceeding as in Step 2 of Scheme I to form a compound of Formula I.

Additional Processes

Compounds of Formula I in which substituent R^1 is NH_2 may be prepared by the reduction of a nitro substituent on the corresponding compound of Formula I; in which R^1 is alkoxy or dialkylamino, by substitution of a corresponding nitro or halo substituent; or in which R^1 is hydroxy, by the de-alkylation of a corresponding alkoxy substituent. Furthermore, compounds of Formula I in which R^1 is Cl, Br, I or NO_2 may be prepared by the introduction of such substituent onto a ring activated by an already present R^1 substituent such as NH_2, NHR, NR_2, OH or alkoxy; or in which R^1 is an acetamido substituent, by the acylation of a corresponding amino substituent. All of the additional processes described above may be performed by methods well known to one of ordinary skill in the art of organic synthesis.

Compounds of Formula I in which u is 1 (compounds of Formula I in which the cyclic amine portion of R^3 is in the N-oxide form) may be prepared by oxidation of the corresponding compound of Formula I in which u is 0, preferably the nonsalt form. The oxidation is carried out at a reaction temperature of approximately 0° C. with an appropriate oxidizing agent and in a suitable inert, organic solvent. Suitable oxidizing agents include peroxy acids such as trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, and m-chloroperoxybenzoic acid. Suitable solvents include halogenated hydrocarbons, e.g., dichloromethane. The oxidation of a compound of Formula I in which u is 0 to the corresponding N-oxide is described in Example 12. Alternatively, the compounds of Formula I in which u is 1 may be prepared using N-oxide derivatives of the starting materials or intermediates, which may be prepared in a similar manner.

Compounds of Formula I in which u is 0 (compounds of Formula I wherein the cyclic amine portion of R^3 is not in the N-oxide form) are also prepared by reduction of the corresponding compound of Formula I in which u is 1. The reduction is carried out under standard conditions with an appropriate reducing agent in a suitable solvent. The mixture is occasionally agitated while the reaction temperature is gradually increased over a range of 0° C. to 80° C. Appropriate reducing agents include sulfur, sulfur dioxide, triaryl phosphines (e.g., triphenyl phosphine), alkali borohydrides (e.g., lithium borohydride, sodium borohydride, etc.), phosphorus trichloride and tribromide. Suitable solvents include acetonitrile, ethanol or aqueous diozane.

As will be apparent to one of ordinary skill in the art, compounds of Formula I may be prepared as individual isomers or mixtures of isomers. Isomers which are diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. For example, diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in

solubility. The separation of a single diastereomer of Formula I is described in Example 13.

Optical isomers can be separated by reacting the racemic mixture with an optically active resolving agent to form a pair of diastereomeric compounds. The isomers are then separated by any of the techniques described above for the separation of diastereomers and the pure optical isomer recovered, along with the resolving agent, by any practical means that would not result in racemization. While resolution of optical isomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred, e.g., crystalline diastereomeric salts. Suitable resolving acids include tartaric acid, o-nitrotartranilic acid, mandelic acid, malic acid, the 2-arylpropionic acids in general, and camphorsulfonic acid.

Individual isomers of compounds of Formula I can also be separated by such methods as direct or selective crystallization or by any other method known to one of ordinary skill in the art. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds of Formula I can be found in Jean Jacques; Andre Collet; Samuel H. Wilen *Enantiomers, Racemates and Resolutions* 1981, John Wiley & Sons, Inc. Alternatively, individual isomers of compounds of Formula I can be prepared using the isomeric forms of the starting materials.

Compounds of Formula I are be converted to the corresponding acid addition salt with a pharmaceutically acceptable inorganic or organic acid. In addition, pharmaceutically acceptable salts may be formed when the acidic proton of R^1 hydroxy substituents present are capable of reacting with inorganic or organic bases. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application.

Compounds of Formula I in the acid addition salt form are converted to the corresponding free base by treatment with a suitable base such as ammonium hydroxide solution, sodium hydroxide or the like. Compounds of Formula I in which R^1 hydroxy substituents form salts are converted to the corresponding free base by treatment with a suitable acid such as hydrochloric acid.

Of the two processes for synthesizing compounds of Formula I described within this application, Scheme I is preferred. While compounds of Formula I may be synthesized by the process described in Scheme II, the alkylation step therein may require severe reaction conditions and is usually restricted to alkylation of unsubstituted amides with primary alkylating agents, e.g., CH_3L.

In summary, the processes for preparing the compounds of Formula I are:

(1) reacting a compound of Formula II with a formylating agent in the presence of a strong base and then acidifying to form a compound of Formula IA or reacting a compound of Formula IV with an alkylating agent of the formula R^3L to form a compound of Formula I;

(2) optionally hydrogenating a compound of Formula IA to form a compound of Formula IB,

(3) optionally reacting with or exchanging substituents present on a compound of Formula I to form an additional substituted compound of Formula I;

(4) optionally converting a salt of a compound of Formula I to the corresponding compound of Formula I;

(5) optionally converting a compound of Formula I to a corresponding pharmaceutically acceptable salt;

(6) optionally oxidizing a compound of Formula I in which u is 0 to form the corresponding N-oxide;

(7) optionally reducing the N-oxide of a compound of Formula I to the corresponding compound of Formula I in which u is 0; or

(8) optionally separating a mixture of isomers of a compound of Formula I into a single isomer.

In any of the above last step processes, a reference to Formula I, IA, IB, II or IV refers to such Formulae wherein n, p, q, R^1, R^2, R^3, R^4, R^5, u, x, y, and z are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

EXAMPLE 1

2,6,7,8,9,9a-Hexahydrocyclohept[cd]isobenzofuran-2-one

The following is the preparation of a compound of Formula III in which

n is 3;

both p and q are 0; and

X and Y are together oxo.

A solution of n-butyllithium/hexanes (2.5M, 32.0 mL, 80.0 mmol) was added in a dropwise fashion over five minutes to a heated solution of 5,6,7,8-tetrahydro-9H-benzocyclohepten-9-ol (4.03 g, 31.9 mmol) in hexane (100 mL). The mixture was maintained at reflux temperature and stirred for 20 hours. The mixture was then cooled to 10° C. and dry carbon dioxide was bubbled through for 5 hours, during which time a white precipitate formed. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate. The aqueous solution was adjusted to pH 2.0 with concentrated hydrochloric acid while being stirred in an ice-water bath. The resulting precipitate was filtered and recrystallized from hexane to give

2,6,7,8,9,9a-hexahydrocyclohept[cd]isobenzofuran-2-one (2.63 g), m.p. 84°–85° C.

EXAMPLE 2

(RS)-N-(1-Azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide

The following is the preparation of a compound of Formula II via Scheme I, Step 1 in which

n is 1;

p and q are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of (RS)-3-amino-1-azabicyclo[2.2.2]octane (1.51 g, 12 mmol) in toluene (20 mL) was added dropwise to a stirred solution of trimethylaluminum (12 mmol) in toluene (6 mL), so that the temperature did not exceed 10° C. The mixture was stirred for 30 minutes, and a solution of ethyl 4-indancarboxylate (2.16 g, 11.3 mmol) in toluene (20 mL) was gradually added. The reaction mixture was heated under reflux for 16 hours, then cooled to room temperature. The reaction mixture was added at 0° C. to aqueous hydrochloric acid (10%, 20 mL). After separation of the layers, the aqueous layer was made basic with 10N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with anhydrous potassium car-

bonate, filtered and evaporated to give 2.42 g (79%) of a white solid. A sample recrystallized from ethyl acetate gave (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide, m.p. 158°–158.5° C. Anal.: Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8:20; N, 10.36. Found: C, 5.95; H, 8.22; N, 10.50.

Proceeding as in Example 2, but replacing (RS)-3-amino-1-azabicyclo[2.2.2]octane with (R)-3-amino-1-azabicyclo[2.2.2]octane gave (R)-N-(1-azabicyclo[2.2.-2]oct-3-yl)-4-indancarboxamide.

Proceeding as in Example 2, but replacing (RS)-3-amino-1-azabicyclo[2.2.2]octane with (S)-3-amino-1-azabicyclo[2.2.2]octane gave (S)-N-(1-azabicyclo[2.2.-2]oct-3-yl)-4-indancarboxamide, m.p. 159°–160° C.; $[\alpha]_D^{25}$ −47.5° (c=0.4, $CHCl_3$).

Proceeding as in Example 2 the following are prepared:

N-(1-azabicyclo[2.2.2]oct-4-yl)-4-indancarboxamide;

N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-4-indancarboxamide;

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-indancarboxamide;

N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-indancarboxamide;

N-(endo-1-azabicyclo[3.3.1]non-4-yl)-4-indancarboxamide;

(RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-5-methoxycarboxamide;

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-5-methoxycarboxamide; and

(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-5-methoxycarboxamide.

EXAMPLE 3

(S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide

The following is the preparation of a compound of Formula II via Scheme I, Step 1 in which

n is 2;

p and q are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid (Ofosu-Asante, K. and Stock, L. M., *J. Org. Chem.* 1986; 51: 5452) (2.06 g, 11.7 mmol), oxalyl chloride (1 mL, 11.7 mmol), and dimethylformamide (0.1 mL) in dichloromethane (20 mL) was stirred at room temperature for one hour. The mixture was then concentrated under reduced pressure, and the residue was dissolved in dichloromethane (20 mL). The resulting solution was added dropwise at 0° C. to a solution of (S)-3-amino-1-azabicyclo[2.2.2]octane (1.48 g, 11.7 mmol) in dichloromethane (20 mL). The solution was stirred at room temperature for 30 minutes, and the solvent was evaporated under vacuum. The residue was dissolved in water and washed with ethyl acetate. The aqueous layer was basified with NH_4OH and extracted with dichloromethane. The dichloromethane was dried with anhydrous potassium carbonate, filtered and then evaporated to afford 2.75 g of white crystals. A sample recrystallized from ethyl acetate/hexane gave (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, m.p. 159°–160° C.; $[\alpha]_D^{25}$ −42.1° (c=0.65, $CHCl_3$).

Proceeding as in Example 3, but replacing 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid with 5,6,7,8-tetrahydro-2-methoxy-1-naphthalenecarboxylic acid gave (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenecarboxamide, m.p. 270°–271° C.

Proceeding as in Example 3, but replacing 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid with 4-chloro-5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid gave (S)-4-chloro-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with 4-amino-1-azabicyclo[2.2.2]octane gave N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with (RS)-3-amino-1-azabicyclo[2.2.2]octane gave (RS)-(1-azabicyclo[2.2.-2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with (R)-3-amino-1-azabicyclo[2.2.2]octane gave (R)-(1-azabicyclo[2.2.-2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with endo-9-methyl-9-azabicyclo[3.3.1]nonane gave N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with endo-8-methyl-8-azabicyclo[3.2.1]octane gave N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalene carboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with exo-8-methyl-8-azabicyclo[3.2.1]octane gave N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with endo-1-azabicyclo[3.3.1]nonane gave N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3 the following are prepared:

N-(exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide; and

N-(exo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

EXAMPLE 4

N-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide

The following is the preparation of a compound of Formula II via Scheme I, Step 1 in which

n is 2;

each p, q and u is 0; and

R^3 is

endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl.

A solution of 5,6,7,8-tetrahydro-1-napthalene-carboxylic acid (571 mg, 3.24 mmol), oxalyl chloride (0.44 mL, 5.0 mmol), and dimethylformamide (0.05 mL) in dichloromethane (20 mL) was stirred at room temperature for one hour. The mixture was then concentrated under reduced pressure and the residue was dissolved in toluene (10 mL). The resulting solution was added dropwise to a stirred mixture of endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane (500 mg, 3.24 mmol) and sodium carbonate (700 mg, 6.5 mmol) in water (5 mL) and toluene (25 mL). After 2 hours the mixture was

diluted with ethyl acetate (100 mL). The layers were separated and the organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford 700 mg of white crystals. A sample recrystallized from ethyl acetate gave N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, m.p. 166°–167° C.

EXAMPLE 5

(RS)-N-(1-Azabicycol[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide

The following is the preparation of a compound of Formula II via Scheme I, Step 1 in which

n is 3;

p and q are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of (RS)-3-amino-1-azabicyclo[2.2.2]octane (1.00 g, 8 mmol)) in toluene (20 mL) was added dropwise to a stirred solution of trimethylaluminum (8 mmol) in toluene (10 mL), so that the temperature did not exceed 10° C. The mixture was stirred for 30 minutes, and a solution of 2,6,7,8,9,9a-hexahydrocyclohept[cd]isobenzofuran-2-one (1.25 g, 6.6 mmol) in toluene (10 mL) was gradually added. The reaction mixture was heated under under reflux 0.5 hours and then cooled to ambient temperature. Water was added gradually until a solid was precipitated, and the mixture was filtered. The solid was washed with ethyl acetate and the combined organic layer was evaporated to give (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide (1.42 g, 68% yield). Crystallization from ethanolic hydrochloric acid gave (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide hydrochloride, m.p. 239° C.

Reduction of (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide (1.42 g, 4.5 mmol) in ethanolic hydrochloric acid (20 ml) with 20% palladium hydroxide on carbon (0.5 g) was carried out at 50 psi for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. Purification of the product by column chromatography (10% methanol in methylene chloride and 1% ammonium hydroxide) gave (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide (0.52 g, 39% yield).

Proceeding as in Example 5 the following are prepared:

N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalene carboxamide;

N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide; and

N-(exo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

EXAMPLE 6

(RS)-2-(1-Azabicylco[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one

The following is the preparation of a compound of Formula I via Scheme I, Step 2 in which

the optional bond is present;

n is 1;

each p, q and u is 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide (2.07 g, 7.7 mmol), prepared as in Example 2, in dry tetrahydrofuran (100 mL) at −70° C. was treated with n-butyllithium (20 mmol). The reaction mixture was stirred at −10° C. for one hour, cooled to −70° C., and dimethylformamide (15 mmol) added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0° C. and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with 10N aqueous sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to give 1.75 g (81% yield) of white crystals. A sample recrystallized from ethyl acetate gave (RS)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one, m.p. 146°–147° C. Anal.: Calcd. for $C_{18}H_{20}N_{20}$: C, 77.11; H, 7.19; N, 9.99%. Found: C, 76.93; H, 7.23; N, 9.90%.

Crystallization from ethanolic hydrochloric acid gave the hydrochloride salt monoethanol adduct, m.p. 188°–190° C. Anal.: Calcd. for $C_{18}H_{20}N_2O$ HCl C_2H_5OH: C, 66.19; H, 7.50; N, 7.72%. Found: C, 66.08; H, 7.55; N, 7.66%.

Proceeding as in Example 6, but replacing (RS)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-indancarboxamide with (S)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-indancarboxamide, prepared as in Example 2, gave (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent-[de]isoquinolin-1-one, m.p. 155.5°–156° C.; $[\alpha]_D^{25}$ +47.1° (c=0.41, $CHCl_3$). Anal.: Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19, N, 9.99%. Found: C, 77.45; H, 7.12; N, 9.84%, and (S)-2-(1-azabicyclo[2.2.-2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one hydrochloride m.p. >285° C.; $[\alpha]_D^{25}$ −12.8°; Anal.: Calcd. for $C_{18}H_{20}N_{20}$.HCl.0.5 H_2O: C, 66.35; H,6.81; N, 8.59%. Found: C, 65.96; H, 6.86; N, 8.33%.

Proceeding as in Example 6, but replacing (RS)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-indancarboxamide with (R)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-indancarboxamide, prepared as in Example 2, gave (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent-[de]isoquinolin-1-one and (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one hydrochloride.

EXAMPLE 7

(S)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one

The following is the preparation of a compound of Formula I via Scheme I, Step 2 in which

the optional bond is present;

n is 2;

each p, q and u is 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of n-butyllithium in hexane (60 mmol) was added dropwise at −70° C. to a solution of (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro1-naphthalenecarboxamide (7.70 g, 21 mmol), prepared as in Example 3, in dry tetrahydrofuran (400 mL). The reaction mixture was stirred at −10° C. for one hour, cooled to −70° C., and dimethylformamide (100 mmol) added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0° C. and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with 10N aqueous sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to give 7.58 g (95% yield) of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro1H-benz[de]isoquinolin-1-one as white crystals; m.p. 117°–118° C.; $[\alpha]_D^{25}$+43.2° (c=0.98, $CHCl_3$).

Crystallization from ethanolic hydrochloric acid gave 9.75 g of the hydrochloride salt monoethanol adduct as white crystals, m.p. >270° C., $[\alpha]_D^{25}$ −8.4° (c=2.4, H_2O). Anal.: Calcd. for $C_{19}H_{22}N_2O$ HCl C_2H_5OH: C, 66.91; H, 7.75; N, 7.43%. Found: C, 66.77; H, 7.65; N, 7.27%.

Crystallization from isopropanolic hydrochloric acid gave the unsolvated hydrochloride salt.

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave (RS)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride m.p. 176°–177° C.

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride, m.p. >275° C., $[\alpha]_D^{25}$+6.8° (c=2, H_2O).

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenecarboxamide, prepared as in Example 3, gave (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-9-methoxy-1H-benz[de]isoquinolin-1-one.

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-4-chloro-1-naphthalenecarboxamide, prepared as in Example 3, gave (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-7-chloro-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one.

EXAMPLE 8

2-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoli-1-one

The following is the preparation of a compound of Formula I via Scheme I, Step 2 in which

the optional bond is present;

n is 2;

each p, q and u is 0; and

R^3 is endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl.

A solution of n-butyllithium in hexane (5 mmol) was added dropwise at −70° C. to a solution of N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide (0.7 g, 2.24 mmol), prepared as in Example 4, in dry tetrahydrofuran (25 mL). The reaction mixture was stirred at −10° C. for one hour, cooled to −70° C., and dimethylformamide (13 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0° C. and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with concentrated ammonium hydroxide and extracted with ethyl acetate (100 mL). The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to give 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolone-1-one.

Crystallization from ethanolic hydrochloric acid gave the hydrochloride salt monoethanol adduct, m.p. 236° C. Anal.: Calcd. for $C_{21}H_{27}ClN_2O$ H_2O: C, 66.92; H, 7.75; N, 7.43%. Found: C 66.45; H, 7.79; N, 7.32%.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide with N-(1-azabicyclo[2.2.2]octan-4-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide, prepared as in Example 3, gave 2-(1-azabicyclo[2.2.2]octan-4-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one hydrochloride, m.p. 335°–337° C.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide with N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide, prepared as in Example 3, gave 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride, m.p. 269°–270°.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide with N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide, prepared as in Example 3, gave 2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride, m.p. >270° C.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide with N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-napththalenecarboxamide, prepared as in Example 3 gave 2-(endo-1-azabicyclo[3.3.1]non-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one hydrochloride, m.p. >360° C.

EXAMPLE 9

(RS)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one

The following is the preparation of a compound of Formula I via Scheme I, Step 2 in which

the optional bond is present;

n is 3;

each p, q and u is 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of n-butyllithium in hexane (2.7 mmol) was added dropwise at −70° C. to a solution of (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocycloheptene-1-carboxamide (0.37 g, 1.2 mmol), prepared as in Example 5, in dry tetrahydrofuran (10 mL). The reaction mixture was stirred at −10° C. for one

hour, cooled to −70° C., and dimethylformamide (1.5 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0° C. and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with aqueous ammonium hydroxide. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated to give 0.15 g (40% yield) of (RS)-2-(1-azabicyclo-[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one as a foam. Crystallization from ethanolic hydrochloric acid gave the hydrochloride salt, m.p. >285° C.

Proceeding as in Example 9 the following are prepared: 2-(1-azabicyclo[2.2.2]oct-4-yl))-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one; 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one;

2-(exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one;

2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one;

2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one

2-(endo-1-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one; and

2-(exo-1-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one.

EXAMPLE 10

(S)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one

The following is the preparation of a diastereomeric mixture of a compound of Formula I via Scheme I, Step 3 in which

the optional bond is absent;

n is 2;

p, q and u are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

(S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydrobenz[de]isoquinolin-1-one (0.32 g, 1.1 mmol), prepared as in Example 3, in acetic acid (5 mL, containing 3 drops of 70% perchloric acid) was reduced with 20% palladium hydroxide on carbon (0.1 g) at 85° C. and 50 psi for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in water (10 mL), basified with ammonium hydroxide solution, and extracted with ethyl acetate. The ethyl acetate was dried over anhydrous potassium carbonate, filtered, and evaporated to give a diastereomeric mixture of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one (0.18 g 0.60 mmol) as a semi-solid. Crystallization from a mixture of ethanolic hydrochloric acid, isopropanol, and ether gave 0.8 g of the hydrochloride salt as white crystals; m.p.>270° C. Anal.: Calcd. for $C_{19}H_{14}N_2O.HCl.0.25\ H_2O$: C, 67.64; H, 7.62; N, 8.30%. Found: C, 67.38; H, 7.70; N, 8.10%.

Proceeding as in Example 10 other compounds of Formula I wherein the optional bond is absent can be prepared.

EXAMPLE 11

2-(1-Azabicyclo[2.2.2]oct-3S-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one

The following is the preparation of a single diastereomer of Formula I in which

the optional bond is absent;

n is 2;

p, q and u are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A diastereomeric mixture of 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one (16.1 9, 54.0 mmol), prepared as in Example 10, was dissolved in ethyl alcohol (100 mL) and hydrochloric acid (59.4 mmol) was added. Crystallization from ethanolic hydrochloric acid and ether gave a diastereomeric mixture of 70% 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one hydrochloride (A) and 30% 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one hydrochloride (B) (10.6 g, 35.6 mmol).

Recrystallization of the 70/30% mixture from ethyl alcohol (100 mL) gave a diastereomeric mixture of 94% A and 6% B (6.24 g, 20.9 mmol), $[\alpha]_D^{25}$ −89.8° (c=0.3, H_2O).

Recrystallization of the 94/6% mixture from ethyl alcohol gave a disastereomeric mixture of 98.9% A and 1.1% B (4.58 g, 15.4 mmol), m.p. 296°-297° C., $[\alpha]_D^{25}$ −98.9° (c=0.53, H_2O).

EXAMPLE 12

(S)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one N-oxide

The following is the preparation of a compound of Formula I via Scheme I, Step 3 in which

the optional bond is present;

n is 2;

u is 1;

both p and q are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

m-Chloroperoxybenzoic acid (0.82g, 4.7 mmol) was added in small portions at 0° C. to a solution of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1-benz[de]isoquinolin-1-one, prepared as in Example 7, (1.16 g, 3.9 mmol) in dichloromethane (50 mL). The reaction mixture was stirred for additional 0.5 hour at 0° C. The solvent was removed under reduced pressure. Purification of the residue by column chromatography (10% methanol in dichloromethane and 1% ammonium hydroxide) gave the N-oxide of (S)-2-(1-azabicyclo-[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one (0.75 g; 62% yield) as an amorphous solid; m.p. 73°-75° C.

Proceeding as in Example 10, other compounds of Formula I wherein u is 1 are prepared.

EXAMPLE 13

The following are representative pharmaceutical formulations containing a compound of Formula I.

ORAL FORMULATION

A representative solution for oral administration contains:

Compound of Formula I	100-1000 mg
Citric Acid Mono hydrate	105 mg
Sodium Hydroxide	18 mg
Flavouring	q.s.
Water	to 100 ml

INTRAVENOUS FORMULATION

A representative solution for intravenous administration contains:

Compound of Formula I	10–100 mg
Dextrose Monohydrate isotonic	q.s. to make
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	to 1.0 ml

TABLET FORMULATION

A representative tablet form of a compound of Formula I may contain:

Compound of Formula I	1%
Microcrystalline cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%

EXAMPLE 14

5-HT_3 Receptor Binding Assay

The following describes an in vitro assay for determining the 5-HT_3 receptor binding affinity of compounds of Formula I. The method is essentially that described by Kilpatrick et al., previously cited, which measures the affinity for 5-HT_3 receptors of the rat cerebral cortex radiolabelled with [^{3}H]quipazine.

Membranes are prepared from the cerebral cortices of rat brains homogenized in 50 mM Tris buffer (pH 7.4 at 4° C.) using a Polytron P10 tissue disrupter (setting 10, 2×10 sec bursts). The homogenate is centrifuged at 48,000×g for 12 min and the pellet obtained is washed, by resuspension and centrifugation, three times in homogenizing buffer. The tissue pellets are resuspended in the assay buffer, and are stored under liquid nitrogen until required.

The binding assays are conducted using a Tris-Krebs assay buffer of the following composition (mM): NaCl, 154; KCl, 5.4; KH_2PO_4, 1.2; $CaCl_2.2H_2O$, 2.5; $MgCl_2$, 1.0; glucose, 11; Tris, 10. Assays are conducted at 25° C. at 7.4 in a final volume of 0.25 ml. Zacopride (1.0 mM) is used to define the non-specific binding (NSB). 5-HT_3 receptors present in rat cortical membranes are labelled using 0.3–0.7 nM [^{3}H]quipazine (specific activity 50–66 Ci/mmol; New England Nuclear) in the presence of 0.1 mM paroxetine to prevent [^{3}H]quipazine binding to 5-HT uptake sites. The rat cortex membranes are incubated with [^{3}H]quipazine in the presence of 10 different concentrations of test compound ranging from 1×10^{-12} to 1×10^{-4} molar. Incubations are conducted for 45 min at 25° C. and are terminated by vacuum filtration over Whatman GF/B glass fiber filtersusing a Brandel 48 well cell harvester. After filtration the filters are washed for 8 sec with 0.1M NaCl. The filters are pretreated with 0.3% polyethyleneimine 18 hr prior to use in order to reduce filter binding of the radioligand. Radioactivity retained on the filters is determined by liquid scintillation counting.

The concentration of test compound producing 50% inhibition of radioligand binding is determined by an iterative curve fitting procedure. Affinities are expressed as the negative logarithm of the IC_{50} value (pIC_{50}). Compounds of Formula I exhibit 5-HT_3 receptor binding affinity, i.e., pIC_{50} values greater than 6.

EXAMPLE 15

5-HT_3 Receptor Antagonist Assay (Von Bezold-Jarisch Reflex)

The following describes an in vivo method for determining the 5-HT_3 antagonist activity of compounds of Formula I. The method is a modified version of that described by Butler et al., Cohen et al., and Fozard, all previously cited, in which the 5-HT_3 selective agonist 2-methyl-5-hydroxytryptamine (2-m-5-HT) is substituted for 5-HT.

Male Sprague-Dawley rats, 250–380 grams, are anesthetized with urethane (1.4 g/kg, i.p.). A tracheotomy is performed and a tube is inserted into the trachea to facilitate respiration. Jugular and femoral veins are canulated for intravenous administration of drug. The duodenum is canulated for intraduodenal administration of drug. Heart rate is monitored by Gould ECG/Biotech amplifiers. After at least a 30 min equilibration period and prior to administration of test compound, control responses to intravenous administration of 2-m-5-HT are determined and a minimal dose producing sufficient and consistent bradycardia is chosen.

Potency

Intravenous challenges to 2-m-5-HT are administered every 12 minutes. Either vehicle or test compound is administered intravenously 5 minutes before each challenge to 2-m-5-HT. Each successive administration of test compound is increased in dosage until responses to 2-m-5-HT are blocked.

Duration

Vehicle or test compound is administered intravenously or intraduodenally and subsequent challenges to 2-m-5-HT are administered at 5, 15, 30, 60, 120, 180, 240, 300 and, in some instances, 360, 420 and 480 minutes post dose.

For both potency and duration studies heart rate (beats/min) is recorded continuously for the duration of the study. Responses to 2-m-5-HT are represented by the peak decrease in heart rate. Effects of test compounds are represented as percent inhibition of the bradycardia induced by 2-m-5-HT. Data are analyzed by a one-way repeated measures ANOVA and followed by pairwise comparison to vehicle control using Fisher's LSD strategy. From a dose-response curve so constructed, an ID_{50} value is obtained to represent the dose that inhibited 50% of the bradycardia induced by 2-m-5HT.

EXAMPLE 16

Ferret, Anti-Emesis Assay

The following describes the procedure for determining the intravenous (i.v.) effects of compounds of Formula I on cisplatin-induced emesis in ferrets.

Adult, male, castrated ferrets are allowed food and water ad libitum both prior to and throughout the testing period. Each animal is randomly chosen and anesthetized with a metofane/oxygen mixture, weighed and assigned to one of three test groups. While anesthetized an incision is made along the ventral cervical region approximately two to four centimeters in length. The jugular vein is then isolated and cannulated with a capped saline filled PE-50 polyethylene tubing. The

cannula is exteriorized at the base of the skull and the incision closed with wound clips. The animals are then returned to their cages and allowed to recover from anesthesia prior to commencement of the study.

Vehicle or test compound is administered i.v. at 1.0 ml/kg and 1.0 mg/kg, respectively. Within 2.0 minutes of the administration of vehicle or test compound, cisplatin is injected i.v. at 1.0 mg/kg. The animals are then observed continuously for a 5 hour period and emetic responses (i.e., vomiting and/or retching) are recorded. For purposes of this example and that of Example 11, vomiting is defined as the successful evacuation of stomach contents and a single episode of retching is defined as rapid and successive efforts to vomit occurring within a one minute time period.

Emetic responses are represented as (1) time to onset of emesis, (2) total vomiting episodes and (3) total retching episodes. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined by Student's t-test when comparing a single treatment group to the vehicle control or by Dunnett's comparative analysis when more than one treatment group is compared to a single vehicle.

Proceeding as in Example 8 but administering the test compounds by oral route, the anti-emetic effects of compounds of Formula I may be evaluated.

EXAMPLE 17

Dog, Anti-Emesis Assay

The following describes the procedure for determining the intravenous (i.v.) effects of compounds of Formula I on cisplatin-induced emesis in dogs.

Male and female dogs (6–15 kg) are fed one cup of dry dog food. One hour following feeding, cisplatin (cis-diamminedichloroplatinum) is administered i.v. at 3 mg/kg. Sixty minutes after the administration of cisplatin, either vehicle or test compound is injected i.v. at 0.1 ml/kg and 1.0 mg/kg, respectively. The dogs are then observed continuously for a 5 hour period and the emetic responses (i.e., vomiting and/or retching) are recorded.

Emetic responses are represented as (1) time to onset of emesis, (2) total vomiting episodes and (3) total retching episodes. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined by Student's t-test when comparing a single treatment group to the vehicle control or by Dunnett's comparative analysis when more than one treatment group is compared to a single vehicle.

EXAMPLE 18

Prokinetic Assay

The following describes an in vivo method of determining the prokinetic activity of the compounds of Formula I by measuring the rate of gastric emptying of test meal in rats. The method is that described by Droppleman et al., previously cited.

Test meal is prepared by slowly adding 20 grams of cellulose gum (Hercules Inc., Wilmington, Del.) to 200 ml of cold distilled water that is being mixed in a Waring blender at approximately 20,000 rpm. Mixing continues until complete dispersion and hydration of the cellulose gum takes place (approximately 5 min). Three beef bouillon cubes are dissolved in 100 ml of warm water and then blended into the cellulose solution followed by 16 g of purified casein (Sigma Chemical Co., St. Louis, Mo.), 8 g of powdered confectioners sugar, 8 g of cornstarch, and 1 g of powdered charcoal. Each ingredient is added slowly and mixed thoroughly resulting in approximately 325 ml of a dark gray to black, homogenous paste. The meal is then refrigerated overnight during which time trapped air escapes. Prior to the assay the meal is removed from the refrigerator and allowed to warm to room temperature.

Mature (170 to 204 g) male Sprague-Dawley rats are deprived of food for 24 hours with water ad libitum. On the morning of the study each animal is weighed and randomly assigned to treatment groups consisting of ten animals per group. Each rat receives either vehicle, test compound or the reference standard metoclopramide by intraperitoneal injection. At 0.5 hours post injection 3.0 ml of test meal is orally administered to each rat with a 5.0 ml disposable syringe. Five test meal samples are weighed on an analytical balance and these weights are averaged to find a mean test meal weight. At 1.5 hours post injection each rat is sacrificed by carbon dioxide asphyxiation and the stomach is removed by opening the abdomen and carefully clamping and cutting the esophagus just below the pyloric sphincter. Taking care not to lose any of the its contents, each stomach is placed on a small, pre-weighed and correspondingly labeled 7 ml weigh boat and immediately weighed on an analytical balance. Each stomach is then cut open along the lesser curvature, rinsed with tap water, gently blotted dry to remove excess moisture and weighed. The amount of test meal remaining in the stomach is represented by the difference between the weight of the full stomach and the weight of the stomach empty. The difference between the amount of test meal remaining and the mean test meal weight represents the quantity of test meal that empties during the 1.5 hour post injection period.

Responses are represented as grams of meal emptied or percent change from control. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined via Dunnett's t-test (Statistical Association Journal, December 1955, 1096–112).

EXAMPLE 19

Anxiolytic Behavior Assay

The following describes an in vivo method for determining anxiolytic activity of compounds of Formula I.

Naive male C5BI/6J mice, 18–20 g, are kept in groups of 10 mice in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

The automated apparatus for detecting changes in exploration is obtained from Omni-Tech Electronics Columbus Ohio and is similar to that of Crawley and Goodwin (1980), as described in Kilfoil et al., cited previously. Briefly, the chamber consists of a plexiglass box (44×21 ×21 cm), divided into two chambers by a black plexiglass partition. The partition dividing the two chambers contains a 13×5 cm opening through which the mouse can easily pass. The dark chamber has clear sides and a white floor. A fluorescent tube light (40 watt) placed above the chambers provides the only illumination. The Digiscan Animal Activity Monitor

System RXYZCM16 (Omni-Tech Electronics) records the exploratory activity of the mice within the test chambers.

Prior to commencement of the study the mice are given 60 min to acclimatize to the laboratory environment. After a mouse receives an intraperitoneal (i.p.) injection of either test compound or vehicle it is returned to its home cage for a 15 min post-treatment period. The mouse is then placed in the center of the light chamber and monitored for 10 minutes.

Anxiolysis is seen as a general increase in exploratory activity in the lighted area. An increase in exploratory activity is relected by increased latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), increase in shuttle activity, increased or unaltered locomotor activity (number of grid lines crossed) and decreased time spent in the dark compartment.

EXAMPLE 20

Withdrawal Anxiety Assay

The following procedure describes a method to determine whether compounds of Formula I effect the anxiety that occurs after abruptly ceasing chronic treatment with drugs of abuse.

Naive male BKW mice (25–30 g) are caged in groups of ten in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light cycle and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

Levels of anxiety are determined by the two-compartment exploratory model of Crawley and Goodwin (see Example 11). Anxiolysis is seen as a general increase in exploratory activity in the lighted area. An increase in exploratory activity is relected by increased latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), increased or unaltered locomotor activity (number of grid lines crossed), increased number of rears and decreased time spent in the dark compartment.

Increased exploratory activity in the lighted area is induced by treating the mice for 14 days with ethanol (8.0 % w/v in drinking water), nicotine (0.1 mg/kg, i.p., twice daily), diazepam (10.0 mg/kg, i.p., twice daily) or cocaine (1.0 mg/kg, i.p., twice daily). Anxiolysis is assessed 1, 3, 7 and 14 days after commencement of the drug regime. The treatment is abruptly ceased and exploratory activity in the lighted area is determined 8, 24 and 48 hours thereafter. Vehicle or test compounds are administered during the withdrawl phase by intraperitoneal injection. Responses are represented as inhibition of the decrease in anxiolytic behavior after the ethanol, cocaine, diazepam or nicotine treatment is ceased.

EXAMPLE 21

Cognitive Enhancement Assay

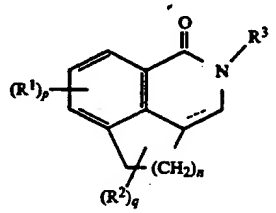
The following describes a model to determine the cognitive enhancing effects of compounds of Formula I.

Young adult and aged BKW mice are caged in groups of ten in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light cycle and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

Levels of anxiety are determined by the two-compartment exploratory model of Crawley and Goodwin (see Example 11). Mice are exposed to the two-compartment test area over a 3 day period. The young mice habituate to the test area by day 3 and spend less time exploring the lighted area, whereas exploratory activity in the lighted area remains constant through day 3 for the aged mice. Exploratory activity is seen as latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), locomotor activity (number of grid lines crossed), number of rears and time spent in the lighted compartment. Vehicle or test compounds are administered to the aged mice by intraperitoneal injection. Cognitive enhancing effects in the aged rats are reflected by a decrease in exploratory activity by day 3.

We claim:

1. A compound of Formula I



I

in which

the dashed line denotes an optional double bond;

n is 1, 2 or 3;

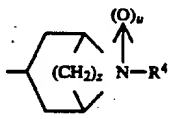
p is 0, 1, 2 or 3;

q is 0, 1 or 2;

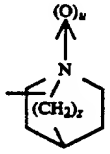
each R^1 is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

each R^2 is lower alkyl; and

R^3 is a group selected from Formulae (a), (b), (c) and (d):



(a)



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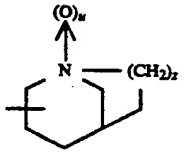
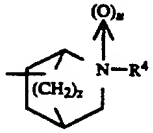


(c)



(d)

in which

u is 0 or 1;

z is 1, 2 or 3; and

R^4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR^5$ where t is 1 or 2 and R^5 is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy; the pharmaceutically acceptable salts, individual isomers, or mixtures of isomers thereof.

2. A compound of claim 1 in which both q and u are 0, p is 0, 1 or 2, each R' is independently selected from halogen, lower alkoxy or amino and R^4 is lower alkyl.

3. A compound of claim 2 in which p is 0, and R^4 is methyl.

4. A compound of claim 3 in which R^3 is one of the following groups:

1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo-[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
endo-1-azabicyclo[3.3.1]non-4-yl; or
exo-1-azabicyclo[3.3.1]non-4-yl.

5. A compound of claim 4 in which the optional bond is present.

6. A compound of claim 5 in which n is 1.

7. A compound of claim 6 in which R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

8. A compound of claim 7 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopenta[-de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

9. A compound of claim 8 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopenta[-de]isoquinolin-1-one hydrochloride.

10. A compound of claim 6 in which R^3 is 8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely, 2-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

11. A compound of claim 10 which is 2-(endo-8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11 which is 2-(endo-8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one hydrochloride.

13. A compound of claim 5 in which n is 2.

14. A compound of claim 13 in which R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

15. A compound of claim 14 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

16. A compound of claim 15 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one hydrochloride.

17. A compound of claim 14 which is (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

18. A compound of claim 17 which is (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one or hydrochloride.

19. A compound of claim 13 in which R^3 is 1-azabicyclo[2.2.2]oct-4-yl, namely 2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

20. A compound of claim 13 in which R^3 is endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl, namely 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one.

21. A compound of claim 13 in which R^3 is 8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely 2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

22. A compound of claim 21 which is 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1one or a pharmaceutically acceptable salt thereof.

23. A compound of claim 21 which is 2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

24. A compound of claim 13 in which R^3 is endo-1-azabicyclo[3.3.1]non-4-yl, namely 2-(endo-1-azabicyclo[3.3.1]non-4-yl)-2,3,5,6-tetrahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

25. A compound of claim 5 in which n is 3.

26. The compound of claim 25 in which R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.-2]oct-3-yl)-1,2,4,5,6,7-hexahydrocycloheptl-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

27. A compound of claim 4 in which the optional bond is absent.

28. A compound of claim 27 in which n is 1.

29. A compound of claim 27 in which n is 2.

30. A compound of claim 29 in which R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo-[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one.

31. A compound of claim 30 which is 2-(1-azabicyclo-[2.2.2]oct-3S-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

32. A compound of claim 31 which is 2-(1-azabicyclo-[2.2.2]oct-3S-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one hydrochloride.

33. A compound of claim 30 which is 2-(1-azabicyclo-[2.2.2]oct-3S-yl)-2,3,3aR,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

34. A compound of claim 33 which is 2-(1-azabicyclo-[2.2.2]oct-3S-yl)-2,3,3aR,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one hydrochloride.

35. A compound of claim 30 which is 2-(1-azabicyclo-[2.2.2]oct-3R-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one a pharmaceutically acceptable salt thereof.

36. A compound of claim 35 which is 2-(1-azabicyclo-[2.2.2]oct-3R-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one hydrochloride.

37. A compound of claim 30 which is 2-(1-azabicyclo-[2.2.2]oct-3R-yl)-2,3,3aR,4,5,6, -hexahydro-1H-benz-[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

38. A compound of claim 37 which is 2-(1-azabicyclo-[2.2.2]oct-3R-yl)-2,3,3aR,4,5,6-hexahydro-1H-benz-[de]isoquinolin-1-one hydrochloride.

39. A compound of claim 27 in which n is 3.

40. A pharmaceutical composition for treating a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain, which composition comprises a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

41. A method for treating a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain in an animal in need of such treatment, which method comprises administering a therapeutically effective amount of a compound of claim 1 to such animal.

42. A method of claim 41 in which the condition is a gastrointestinal disorder treatable with prokinetic agents.

43. A method of claim 41 in which the condition is pain.

44. A method of claim 41 in which the condition is anxiety/depressive state.

45. A method of claim 44 in which the condition is the side effects caused by withdrawal from an addictive substance.

46. A method of claim 41 in which the condition is emesis.

47. A method of claim 46 in which the condition is emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, or recovering from surgical anesthesia or undergoing drug therapy in general in which a significant side effect is emesis.

48. A method of claim 47 in which the compound is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

49. A method of claim 47 in which the compound is 2-(3S-1-azabicyclo-[2.2.2]oct-3-yl-2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

50. A method of claim 42 in which the compound is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one.

* * * * *

ATTACHMENT C
(Copies of maintenance fee statements and fee payment window information for US Patent No. 5,202,333)

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1	5,202,333	183	990	0	07/704,565	04/13/93	05/22/91	04	NO	PAID

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1	5,202,333	184	1900	0	07/704,565	04/13/93	05/22/91	08	NO	PAID

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Patent 5202333 **Application Number:** 07704565

	4th Year	8th Year	12th Year
Opening	04/15/1996	04/13/2000	04/13/2004
Surcharge	10/16/1996	10/16/2000	10/14/2004
Closing	04/14/1997	04/13/2001	04/13/2005

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ATTACHMENT D
(Copy of Notice of Recordation and recorded assignment
from Jacob Berger et al. to Syntex (U.S.A.) Inc.
for US Application No. 07/704,565 (Patent No. 5,202,333))

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PALO ALTO, CA 94303

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CLARK, ROBIN D.

ASSIGNOR: DOC DATE: 08/29/91
EGLEN, RICHARD M.

ASSIGNOR: DOC DATE: 08/29/91
SMITH, WILLIAM L.

ASSIGNOR: DOC DATE: 08/29/91
WEINHARDT, KLAUS K.

RECORDATION DATE: 09/13/91 NUMBER OF PAGES 004 REEL/FRAME 5829/0428

DIGEST :ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
SYNTEX (U.S.A.) INC.
A CORPORATION OF DE
P.O. BOX 10850
3401 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94303

SERIAL NUMBER	7-704565	FILING DATE	05/22/91
PATENT PATENT		ISSUE DATE	00/00/00

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Inventor(s): Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt

Assignee: Syntex (U.S.A.) Inc.

Serial No.: 07/704,565

Filing Date: May 22, 1991

Case No.: 26890-CIP

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If additional space is needed attach separate sheet.

Wayne W. Montgomery (Signature) Reg. No. 35,016

FOR PROMPT, ACCURATE SHIPMENT PLEASE COMPLETE THE FOLLOWING MAILING LABEL—PLEASE PRINT OR TYPEWRITE

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
OFFICIAL BUSINESS
RETURN AFTER FIVE DAYS

CASE # 26890-CIP
YOUR ORDER NO.
996

NAME SYNTEX (U.S.A.) INC. - PATENT DEPT. A2-200
STREET ADDRESS 3401 Hillview Avenue P.O. Box 10850
CITY, STATE, ZIP CODE Palo Alto, California 94303

Case 26890-CIP

ASSIGNMENT

WHEREAS, we, Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, of Los Altos Hills, California; Palo Alto, California; Mountain View, California; Sunnyvale, California; and San Francisco, California, respectively, have invented certain new and useful improvements (the "Invention") in

TRICYCLIC 5-HT_3 RECEPTOR ANTAGONISTS

which is described in an application for Letters Patent of The United States of America executed by us on September 5, 1991; August 29, 1991; August 29, 1991; August 29, 1991; and August 29, 1991, respectively; and filed in the United States Patent and Trademark Office on May 22, 1991, under Serial No. 07/704,565;

AND WHEREAS, SYNTEX (U.S.A.) INC., a corporation of Delaware, having an address at 3401 Hillview Avenue, P.O. Box 10850, Palo Alto, California 94303, is desirous of acquiring an interest therein and in the Letters Patent to be obtained therefore from the United States;

NOW, THEREFORE, in exchange for good and valuable consideration, the receipt and sufficiency are hereby acknowledged, we, Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, by these presents do hereby assign, sell and transfer unto said SYNTEX (U.S.A.) INC., for the territory of The United States of America and for all foreign countries, the full and exclusive right, title and interest, including all rights under the Paris Convention for the Protection of Industrial Property, in the Invention, as described in the specification of the application for Letters Patent of The United States under Serial No. 07.704,543, or in any continuation, division, reissue, reexamination or extension thereof and any legal equivalent thereof in a country foreign to the United States of America; said Invention, application and Letters Patent to be held and enjoyed by said SYNTEX (U.S.A.) INC., for its own use and behoof, and for the use and behoof of its successors, assigns and legal representatives, to the full end of the term for which said Letters Patent may be granted as fully and entirely as the same would have been held by us had this assignment and sale not been made. This assignment is effective as of May 22, 1991.

IN WITNESS WHEREOF, we, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, have read and understood this Assignment document for the Invention described in the application for Letters Patent of The United States of America, Serial No. 07/704,565, and agree hereto, as indicated by our signatures set forth below.

Signature: Robin D. Clark — Date: 8-29-91
Robin D. Clark

Signature: Richard M Eglen — Date: August 29th 1991
Richard M. Eglen

Signature: William L. Smith — Date: 29 August 1991
William L. Smith

Signature: Klaus K. Weinhardt — Date: 8/29/91
Klaus K. Weinhardt

STATE OF CALIFORNIA }
} ss.
COUNTY OF SANTA CLARA }

On this the 29th day of August, 1991, before me, Jean M. Bruder, the undersigned Notary Public, personally appeared Robin D. Clark, Richard M. Eglen, William L. Smith and Klaus K. Weinhardt.

☐ personally known to me

☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) are subscribed to the within instrument, and acknowledged that they executed it.

WITNESS my hand and official seal.

Jean M. Bruder
Notary Public

OFFICIAL NOTARY SEAL
JEAN M. BRUDER
Notary Public — California
SANTA CLARA COUNTY
My Comm. Expires APR 17 1995

IN WITNESS WHEREOF, I, Jacob Berger, have read and understood this Assignment document for the Invention described in the application for Letters Patent of The United States of America, Serial No. 07/704,565, and agree hereto, as indicated by my signatures set forth below.

Signature: Jacob Berger Date: 9-5-91
Jacob Berger

STATE OF CALIFORNIA }
} ss.
COUNTY OF SANTA CLARA }

On this the 5th day of Sept., 1991, before me, Jean M. Bruder, the undersigned Notary Public, personally appeared Jacob Berger

☐ personally known to me

☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is subscribed to the within instrument, and acknowledged that he executed it.

WITNESS my hand and official seal.

RECORDED
PATENT AND TRADEMARK
OFFICE
SEP 13 1991

Jean M. Bruder
Notary Public

OFFICIAL NOTARY SEAL
JEAN M. BRUDER
Notary Public — California
SANTA CLARA COUNTY
My Comm. Expires APR 17 1995

REEL 5029 FRAME 431

ATTACHMENT E
(Copy of Notice of Recordation and recorded Certificate of Merger
of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC
for US Patent No. 5,202,333)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JULY 10, 2003

PTAS

HELLER EHRMAN WHITE & MCAULIFFE LLP
DEREK P. FREYBERG
MENLO PARK, CA 94025-3506

700035674A

700035674A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 07/09/2003

REEL/FRAME: 013782/0352
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SYNTEX (U.S.A.) INC.

DOC DATE: 05/30/2000

ASSIGNEE:
SYNTEX (U.S.A.) LLC
3431 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304

SERIAL NUMBER: 07704565
PATENT NUMBER: 5202333

FILING DATE: 05/22/1991
ISSUE DATE: 04/13/1993

LAZENA MARTIN, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

07/09/2003
700035674

RECORDATION FORM COVERSHEET (PATENTS)

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being transmitted by facsimile to the US PTO at (703) 306-5995 on July 9, 2003.

Derek P. Freyberg, Reg. No. 29,250 — 7/9/03 Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Please record the attached document:

1. Name of conveying party:	Syntex (U.S.A.) Inc.
2. Name and address of receiving party:	Syntex (U.S.A.) LLC 3431 Hillview Avenue Palo Alto CA 94304
3. Nature and date of conveyance:	Merger; signed May 30, 2000
4. Application or patent number:	Patent No. 5,202,333
5. Correspondence address:	Heller Ehrman White & McAuliffe LLP 275 Middlefield Road Menlo Park CA 94025-3506 Tel: 650.324.7000; fax: 650.324.0638
6. Recordation fee and authorization:	Fee $40; charge to Deposit Account No. 08-1641 (ref. 13265-1163)
7. Total number of pages:	4

8. Statement and signature:
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Derek P. Freyberg
Reg. No. 29,250

Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park CA 94025-3506
(650) 324-7014
July 9, 2003

SV 444525 v1 Prev SV 372264
07/09/03 10:43 AM

CH $40.00 081641 5202333

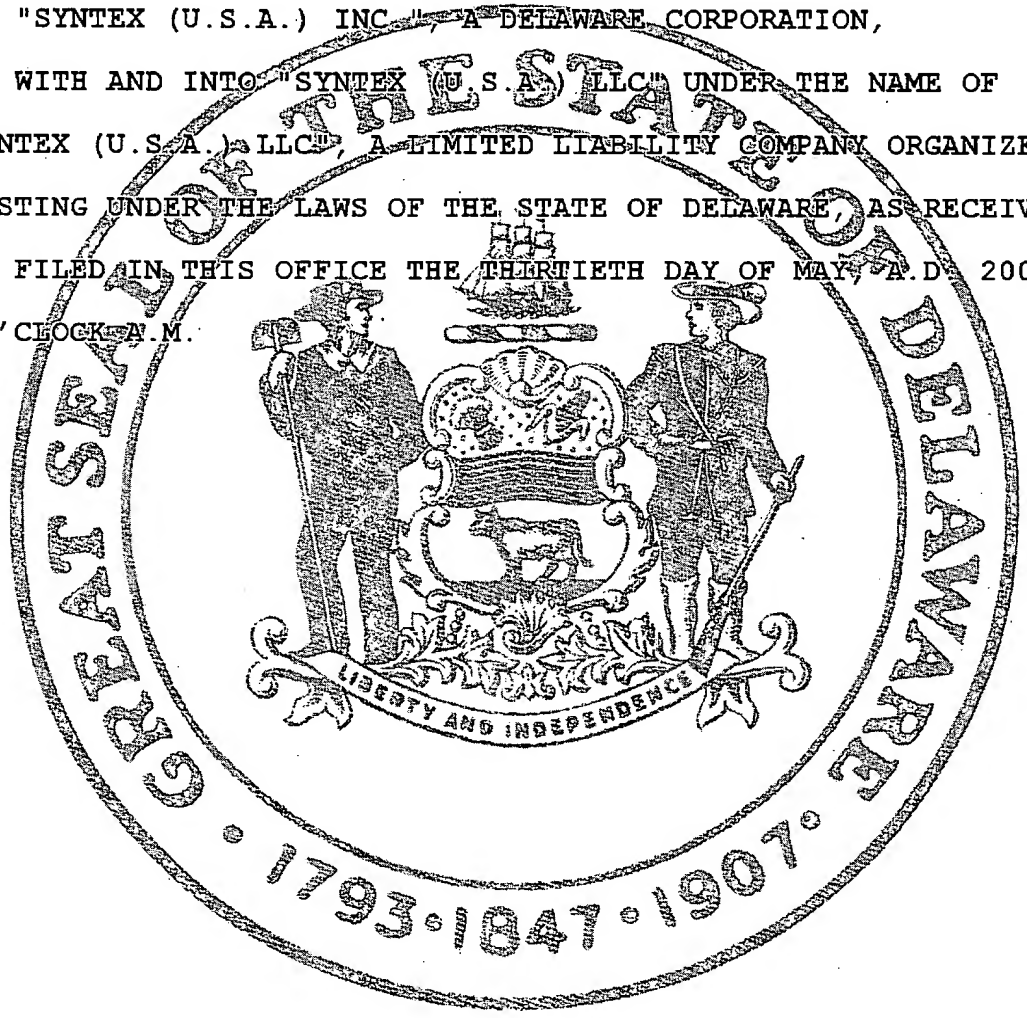
State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"SYNTEX (U.S.A.) INC.", A DELAWARE CORPORATION,

WITH AND INTO "SYNTEX (U.S.A.) LLC" UNDER THE NAME OF "SYNTEX (U.S.A.) LLC", A LIMITED LIABILITY COMPANY ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE THIRTIETH DAY OF MAY, A.D. 2000, AT 9 O'CLOCK A.M.



3205906 8100M

001454182

AUTHENTICATION: 0664301

Edward J. Freel, Secretary of State

DATE: 09-08-00

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 05/30/2000
001271741 - 3205906

CERTIFICATE OF MERGER
OF
SYNTEX (U.S.A.) INC.
INTO
SYNTEX (U.S.A.) LLC

(Under Section 264 of the General Corporation Law of the State of Delaware and Section 18-209 of the Delaware Limited Liability Company Act)

The undersigned limited liability company formed and existing under and by virtue of the Delaware Limited Liability Company Act, 6 Del.C. § 18-101, *et seq.* (the "Act").

DOES HEREBY CERTIFY:

FIRST: The name and jurisdiction of formation or organization of each of the constituent entities which is to merge are as follows:

Name	Jurisdiction of Formation or Organization
Syntex (U.S.A.) Inc.	Delaware
Syntex (U.S.A.) LLC	Delaware

SECOND: An Agreement and Plan of Exchange and Merger has been approved, adopted, certified, executed and acknowledged by each of the constituent entities in accordance with Section 264(c) of the General Corporation Law of the State of Delaware, 8 Del.C. § 191m *et seq.* (the "GCL"), Section 18-209 of the Act and, with respect to Syntex (U.S.A.) Inc., Section 228 of the GCL.

THIRD: The name of the surviving Delaware limited liability company is Syntex (U.S.A.) LLC.

FOURTH: The merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC shall be effective as of the close of business on the day the filing of this Certificate of Merger with the Secretary of State of the State of Delaware is made.

FIFTH: The executed Agreement and Plan of Exchange and Merger is on file at an office of the surviving Delaware limited liability company. The address of such place of business of the surviving Delaware limited liability company is 3401 Hillview Avenue, Palo Alto, California 94304.

SIXTH: A copy of the Agreement and Plan of Exchange and Merger will be furnished by the surviving Delaware limited liability company, on request and without cost, to any member of Syntex (U.S.A.) LLC, and to any stockholder of Syntex (U.S.A.) Inc.

SYNTEX (U.S.A.) LLC

By: _____
Name: Nancy M. Cohen
Title: Vice President & Secretary

ATTACHMENT F
(Copy of Notice of Recordation and Certificate of Amendment
changing name of Syntex (U.S.A.) LLC to Roche Palo Alto LLC
for US Patent No. 5,202,333)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JULY 11, 2003

PTAS

HELLER EHRMAN WHITE & MCAULIFFE LLP
DEREK P. FREYBERG
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

700035848A

700035848A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 07/10/2003

REEL/FRAME: 013782/0874
NUMBER OF PAGES: 3

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SYNTEX (U.S.A.) LLC

DOC DATE: 12/20/2000

ASSIGNEE:
ROCHE PALO ALTO LLC
3431 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304

SERIAL NUMBER: 07704565
PATENT NUMBER: 5202333

FILING DATE: 05/22/1991
ISSUE DATE: 04/13/1993

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

07/10/2003
700035848

RECORDATION FORM COVERSHEET (PATENTS)

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being transmitted by facsimile to the US PTO at (703) 306-5995 on July 10, 2003.

Derek P. Freyberg, Reg. No. 29,250 — 7/10/03 Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Please record the attached document:

1. Name of conveying party:	Syntex (U.S.A.) LLC
2. Name and address of receiving party:	Roche Palo Alto LLC 3431 Hillview Avenue Palo Alto CA 94304
3. Nature and date of conveyance:	Change of name; signed December 20, 2000
4. Application or patent number:	Patent No. 5,202,333
5. Correspondence address:	Heller Ehrman White & McAuliffe LLP 275 Middlefield Road Menlo Park CA 94025-3506 Tel: 650.324.7000; fax: 650.324.0638
6. Recordation fee and authorization:	Fee $40; charge to Deposit Account No. 08-1641 (ref. 13265-1163)
7. Total number of pages:	3.

8. Statement and signature:
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Derek P. Freyberg
Reg. No. 29,250

Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park CA 94025-3506
(650) 324-7014
July 10, 2003

SV 444762 v1 Prev SV 372264
07/10/03 10:02 AM

CH $40.00 081641 5202333

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "SYNTEX (U.S.A.) LLC", CHANGING ITS NAME FROM "SYNTEX (U.S.A.) LLC" TO "ROCHE PALO ALTO LLC", FILED IN THIS OFFICE ON THE TWENTY-THIRD DAY OF DECEMBER, A.D. 2002, AT 4 O'CLOCK P.M.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

3205906 8100

020794267

AUTHENTICATION: 2168192

DATE: 12-24-02

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 04:00 PM 12/23/2002
020794267 – 3205906

CERTIFICATE OF AMENDMENT

OF

SYNTEX (U.S.A.) LLC

1. The name of the limited liability company is, upon the effective time of this amendment, Roche Palo Alto LLC.

2. The Certificate of Formation of the limited liability company is hereby amended as follows:

The paragraph labeled "FIRST" is changed to read, The name of the limited liability company formed hereby is Roche Palo Alto LLC.

The heading is changed to read, CERTIFICATE OF FORMATION OF ROCHE PALO ALTO LLC.

3. This Certificate of Amendment shall be effective on 12:01 am, January 1, 2003.

IN WITNESS WHEREOF, the undersigned has executed this Certificate of Amendment of Syntex (U.S.A.) LLC this 20th day of December, 2002.

Nancy M. Cohen
Vice President, Secretary

DE084 - 3/12/2002 C T System Online

COLDENN 119635 v01
12/19/02 at 11:14 AM

TOTAL P.02

ATTACHMENT G

(Copy of authorization from Helsinn Healthcare SA to Roche Palo Alto LLC
to rely upon the activities of Helsinn Healthcare SA before the US Food and Drug Administration
in making its application for extension of patent term)

ATTACHMENT H
(Copy of FDA Approval Letter and label for Aloxi™, NDA 21-372, July 25, 2003)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-372

Helsinn Healthcare S.A.
c/o August Consulting
Attention: Craig Lehmann, Pharm. D.
515 Capital of Texas Highway, Suite 150
Austin, TX 78746

Dear Dr Lehmann:

Please refer to your new drug application (NDA) dated September 26, 2002, received September 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aloxi™ (palonosetron hydrochloride injection).

We acknowledge receipt of your submissions dated October 11 and November 21, 2002 and January 24, April 9, April 24, May 15, June 6, June 9, June 13, June 16, June 18, June 20, June 25, July 1, July 17, and July 22, 2003.

This new drug application provides for the use of Aloxi™ (palonosetron hydrochloride injection) for:
1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Please note that, based on the primary stability data submitted, we are granting a 24-month expiration period for this product. When additional stability data are available, an extension of the expiration period may be requested by submission of a prior approval supplemental new drug application.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (carton label submitted June 25, 2003 and immediate container label submitted July 1, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-372.**" Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. We acknowledge your June 26, 2003 "Proposed Pediatric Study Request" submitted under IND 39,797. We are reviewing your submission and will respond to your proposal in a separate letter. FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, we request that you initiate a 15-day report [21 CFR 314.80(c)] for each of the following:

- All spontaneous reports of constipation requiring hospitalization or emergency room visit
- All spontaneous reports of possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit
- All spontaneous reports of any cardiovascular adverse event

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics

qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/rump.htm.

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Project Manager at (301) 827-7473.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

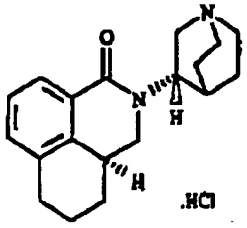
Enclosure

Aloxi™ (Palonosetron Hydrochloride) Injection

Helsinn Healthcare S.A. NDA 21-372 Palonosetron: Proposed Labeling

DESCRIPTION

Aloxi[1] (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.
Aloxi injection is a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration. Each 5-ml vial of Aloxi injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration. The pH of the solution is 4.5 to 5.5.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Palonosetron is a selective 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

---

[1] Pending trademark of Helsinn Healthcare SA
Lugano, Switzerland

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in clinical trials. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration. In clinical trials, the dose-response relationship to the QTc interval has not been fully evaluated.

Pharmacokinetics

After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3–90 μg/kg in healthy subjects and in cancer patients. Following single IV dose of palonosetron at 3 μg/kg (or 0.21 mg/70 kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5.6 ± 5.5 ng/mL and mean AUC was 35.8 ± 20.9 ng-hr/mL.

Distribution

Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Elimination

After a single intravenous dose of 10 μg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects the total body clearance of palonosetron was 160 ± 35 mL/h/kg and renal clearance was 66.5± 18.2 mL/h/kg . Mean terminal elimination half-life is approximately 40 hours.

Special Populations

Geriatrics

Population PK analysis and clinical safety and efficacy data did not reveal any differences between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). No dose adjustment is required for these patients.

Race

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 µg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

Renal Impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

Hepatic Impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

Drug-Drug Interactions

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CPY2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore the potential for clinically significant drug interactions with palonosetron appears to be low.

A study in healthy volunteers involving single-dose IV palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, Aloxi injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

CLINICAL STUDIES

Efficacy of single-dose palonosetron injection in preventing acute and delayed nausea and vomiting induced by both moderately and highly emetogenic chemotherapy was studied in three Phase 3 trials and one Phase 2 trial. In these double-blind studies, complete response rates (no emetic episodes and no rescue medication) and other efficacy parameters were assessed through at least 120 hours after

administration of chemotherapy. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also studied.

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose IV Aloxi with either single-dose IV ondansetron (study 1) or dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin ≤ 50 mg/m², cyclophosphamide < 1500 mg/m², doxorubicin > 25 mg/m², epirubicin, irinotecan, and methotrexate > 250 mg/m². Concomitant corticosteroids were not administered prophylactically in study 1 and were only used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naïve to previous chemotherapy (54%). The mean age was 55 years.

Highly Emetogenic Chemotherapy

A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose IV palonosetron from 0.3 to 90 µg/kg (equivalent to < 0.1 mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin ≥ 70 mg/m² or cyclophosphamide > 1100 mg/m²). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 0.25 mg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

A Phase 3, double-blind trial involving 667 patients compared single-dose IV Aloxi with single-dose IV ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin ≥ 60 mg/m², cyclophosphamide > 1500 mg/m², and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

Efficacy Results

The antiemetic activity of Aloxi was evaluated during the acute phase (0-24 hours) [Table 1], delayed phase (24-120 hours) [Table 2], and overall phase (0-120 hours) [Table 3] post-chemotherapy in Phase 3 trials.

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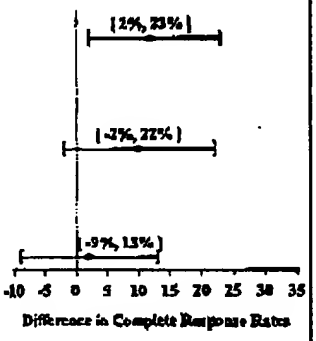
Table 1: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval Aloxi minus Comparator [c]
Moderately Emetogenic	1	Aloxi 0.25 mg	189	81	0.009	
		Ondansetron 32 mg IV	185	69		
	2	Aloxi 0.25 mg	189	63	NS	
		Dolasetron 100 mg IV	191	53		
Highly Emetogenic	3	Aloxi 0.25 mg	223	59	NS	
		Ondansetron 32 mg IV	221	57		



a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between Aloxi and comparator.

These studies show that Aloxi was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT3 receptor antagonists has not been adequately demonstrated in the acute phase.

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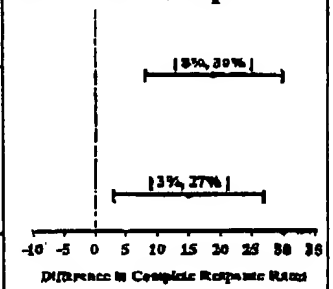
Table 2: Prevention of Delayed Nausea and Vomiting (24-120 hours): Complete Response Rates

Chemo-therapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval Aloxi minus Comparator [c]
Moderately Emetogenic	1	Aloxi 0.25 mg	189	74	<0.001	
		Ondansetron 32 mg IV	185	55		
	2	Aloxi 0.25 mg	189	54	0.004	
		Dolasetron 100 mg IV	191	39		

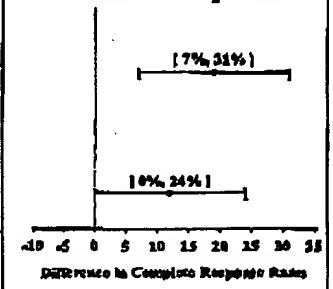


a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between Aloxi and comparator.

These studies show that Aloxi was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Table 3: Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

Chemo-therapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval Aloxi minus Comparator [c]
Moderately Emetogenic	1	Aloxi 0.25 mg	189	69	<0.001	
		Ondansetron 32 mg IV	185	50		
	2	Aloxi 0.25 mg	189	46	0.021	
		Dolasetron 100 mg IV	191	34		



a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between Aloxi and comparator.

These studies show that Aloxi was effective in the prevention of nausea and vomiting throughout the 120 hours (5 days) following initial and repeat courses of moderately emetogenic cancer chemotherapy.

INDICATIONS AND USAGE

Aloxi is indicated for:

1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

CONTRAINDICATIONS

Aloxi is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

PRECAUTIONS

General

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

Although palonosetron has been safely administered to 192 patients with pre-existing cardiac impairment in the Phase 3 studies, Aloxi should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. In 3 pivotal trials, ECGs were obtained at baseline and 24 hours after subjects received palonosetron or a comparator drug. In a subset of patients ECGs were also obtained 15 minutes following dosing. The percentage of patients (< 1%) with changes in QT and QTc intervals (either absolute values of > 500 msec or changes of > 60 msec from baseline) was similar to that seen with the comparator drugs.

Drug Interactions

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions section).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150 to 289 times the human exposure (AUC= 29.8 ng·h/ml) at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human

exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.
Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy, Teratogenic Effects: Category B

Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, palonosetron should be used during pregnancy only if clearly needed.

Labor and Delivery

Palonosetron has not been administered to patients undergoing labor and delivery, so its effects on the mother or child are unknown.

Nursing Mothers

It is not known whether palonosetron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use

Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects but greater sensitivity in some older individuals cannot be ruled out. No dose adjustments or special monitoring are required for geriatric patients.

ADVERSE REACTIONS

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with Aloxi and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 2% of patients in these trials (Table 4).

Table 4: Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Aloxi 0.25 mg (N=633)	Ondansetron 32 mg IV (N=410)	Dolasetron 100 mg IV (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 µg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg IV dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of Aloxi to adult patients receiving concomitant cancer chemotherapy:

Cardiovascular: 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation . In many cases, the relationship to Aloxi was unclear.

Dermatological: < 1%: allergic dermatitis, rash.

Hearing and Vision: < 1% motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal system: 1%: diarrhea, < 1%: dyspepsia, abdominal pain, dry mouth, hiccups and flatulence.

General: 1%: weakness, < 1%: fatigue, fever, hot flash, flu-like syndrome.

Liver: < 1%: transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic: 1%: hyperkalemia, < 1%: electrolyte fluctuations, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: < 1%: arthralgia.

Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paraesthesia.

Psychiatric: 1%: anxiety, < 1%: euphoric mood.

Urinary System: < 1%: urinary retention.

Vascular: < 1%: vein discoloration, vein distention.

Overdosage

There is no known antidote to Aloxi. Overdose should be managed with supportive care. Fifty adult cancer patients were administered palonosetron at a dose of 90 µg/kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 0.25 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed. Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

DOSAGE AND ADMINISTRATION

Dosage for Adults

The recommended dosage of Aloxi is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of Aloxi™ within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

Use in Geriatric Patients and in Patients with Impaired Renal or Hepatic Function

No dosage adjustment is recommended.

Dosage for Pediatric Patients

A recommended intravenous dosage has not been established for pediatric patients.

Administration

Aloxi is to be infused intravenously over 30 seconds. Aloxi should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of Aloxi.

Stability

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

HOW SUPPLIED

Aloxi (palonosetron hydrochloride), 0.25 mg (free base) in 5 ml, is supplied as a single-use sterile, clear, colorless solution in glass vials ready for intravenous injection.
Store at controlled temperature of 20–25°C (68°F–77°F). Excursions permitted to 15–30 °C (59-86°F). Protect from freezing. Protect from light.
NDC Number 58063-797-25
Prescribing information as of XXXX, 2003
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Julie Beitz
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